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ACUTE HEPATITIS B IN A PATIENT PREVIOUSLY POSITIVE FOR ANTIBODY TO SURFACE ANTIGEN (ANTI-HBs) DETERMINED BY RADIOIMMUNOASSAY. CASE REPORT AND REVIEW OF THE LITERATURE

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SUMMARY

The determination of anti-HBs as a screening test before vaccination has been advisable in order to encounter immune individuals that don't need to receive vaccine protection. A case-report is presented and three other cases are reviewed from the literature. Anti-HBs was positive in these health-care personnels that developped typical acute B hepatitis. Different subtyping involving the d/y determinants were found in the first case, but false-positive anti-HBs even with high titres, determined by RIA, were found in the other cases. Concomitant determination of anti-HBc or absence of screening tests seem to be more reasonable policies until a low-cost and risk-free vaccine is produced.

INTRODUCTION

Hepatitis B is a widespread infection all over the world. Hospital personnels as well as drug addicts and male homosexuals are the most important groups with the higher risk of getting the infection. This high risk population, more frequently in contact with the B virus, can develop a subclinical infection, which would naturally protect them against hepatitis B. Following this reasoning and taking in account that B vaccine, made up of human serum, is expensive and not entirely free of eventual desease transmission, the determination of anti-HBs as a screening test pre-vaccination would be advisable, and has been recomended by many Authors [7,8].

Herein a case report of a physician who already had anti-HBs in the serum and developed an acute B hepatitis is described.

CASE REPORT

E.S., female, 40 years old, physician. The first determination of virus B markers was made in April 1981 during a research screening in hospital personnel [12] and at that time her serum was positive for anti-HBs. Contamination occurred in the seventeenth of March 1983, by needle stick, while taking blood sample from a HBsAg positive and also HBeAg positive patient with persistent chronic hepatitis. Preventive measures, such as pos-exposure vaccination or administration of hyperimmune gammaglobulin, were not carried out. In the 23rd of June symptoms of dizziness and weakness appeared, being associated with coluria in the 28th, when blood samples were taken for transaminases determinations. As they were above 10 times the upper normal limit a diagnosis of acute hepatitis was made and serum taken for viral markers determinations.

Symptoms persisted and worsened in the following weeks with deep jaundice, intense anorexia and weight loss. Liver was palpable 2 cm bellow the right costal margin, but spleen was not detectable. Sequential laboratorial data are summarized in Table I and Graphic 1 illustrates the evolution of main parameters.

Complete recovery with negativation of the HBsAg was achieved after 12 weeks and one

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year after (August/84) biochemical examinations re-assured this recovery. Virus B markers, determined by Enzymeimmunoassay (ELISA), showed HBsAg negative and both anti-HBs and anti-HBc positive. Re-testing the serum taken at the onset of acute hepatitis the anti-HBs remained positive by RIA but it turned to be negative by ELISA.

TABLE I
Laboratorial data of the case-report

Data / Exam	1983 06/28	07/05	07/12	07/19	07/29	08/12	08/26	09/09	09/23	1984 08/14	Upper normal values
ALT	645	711	1052	370	277	225	62	16	08	05	25uI
AST	294	496	798	440	551	247	54	15	11	10	20uI
GGT	17	21	16		30	28				07	18uI
T. Bil.	1,46	2,98	15,48	20,51	17,16	6,08	2,82	2,37	1,33	0,5	1,2 mg%
Dir. Bil.	0,94	1,75	10,23	15;83	14,25	5,10	2,60	1,35	1,16	0,4	0,4 mg%
Prothr. Activity	99%	92%	98%	100%	—	100%					80-100%
Alb.	3,8						3,52			3,92	3,5 to 5,2g%
Alpha 1 G	0,36						0,36			0,25	0,1 to 0,3g%
Alpha 2 G	0,48						0,55			0,70	0,4 to 0,8g%
Beta G	0,66						0,84			0,87	0,5 to 0,9g%
Gama G	1,20						1,63			1,26	0,8 to 1,5g%
HBsAg	(+)							(+)	—	—	
Anti-HBc	(+)									(+)	
Anti-HBs	(+)									(+)	
HBe Ag	(+)				—	(—)					
Anti-HBe	(—)				—	(+)					

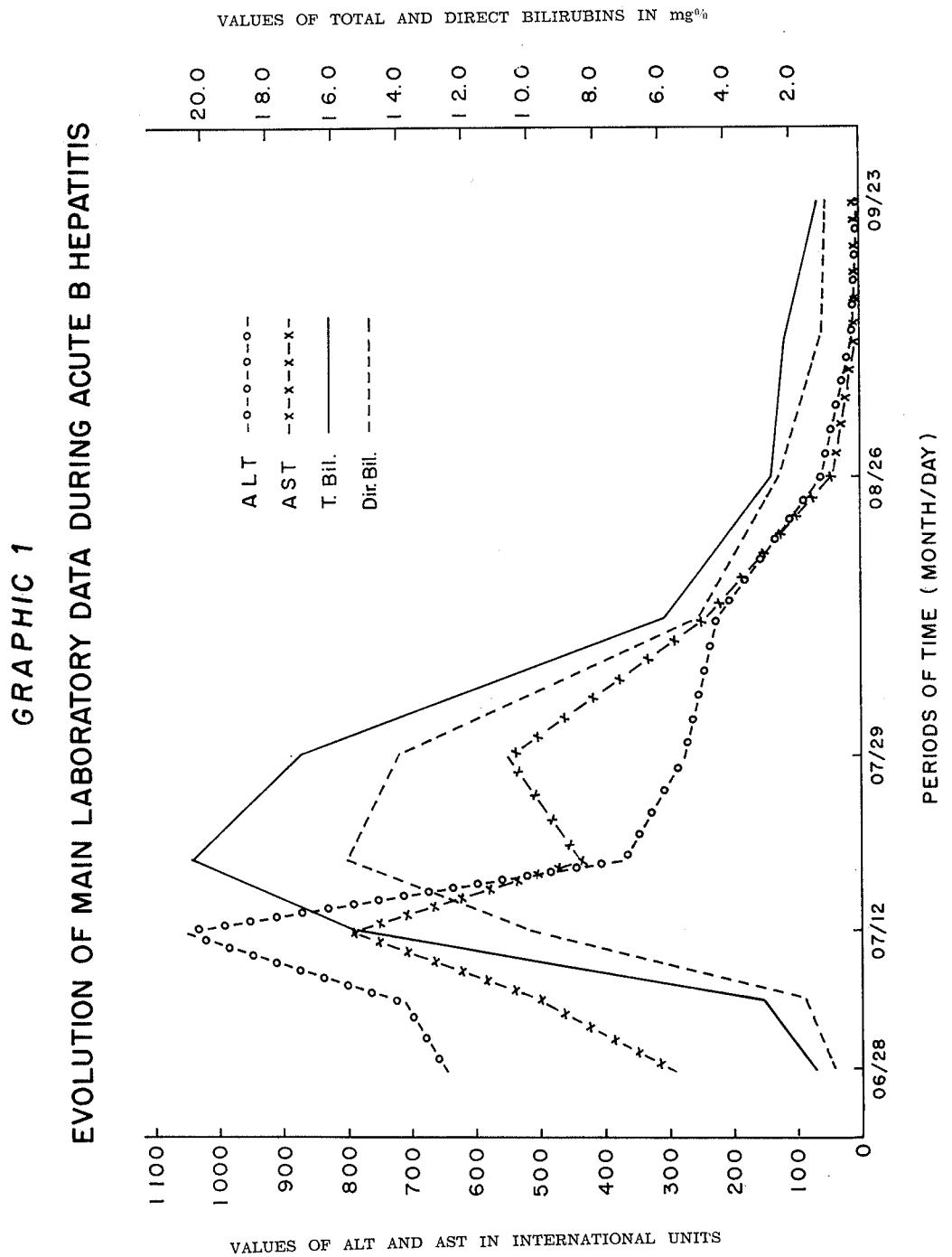
ALT = Alanineaminotransferase
AST = Aspartatoaminotransferase
GGT = Gamaglutamiltransferase
T. Bil. = Total bilirubin
Dir. Bil. = Direct bilirubin
Prothr. Activity = Prothrombin Activity
Alb. = serum albumin
G = Globulins
HBsAg = Hepatitis B surface antigen
Anti-HBc = Antibody to hepatitis B core
Anti-HBs = Antibody to hepatitis B surface
HBe Ag = Hepatitis B "e" antigen
Anti-HBe = Antibody to hepatitis B "e antigen"

COMMENTS

It is well known that in the course of a typical virus B hepatitis the positivity of anti-HBc indicates present infection whereas the development of anti-HBs, after 8 to 12 weeks, is the usual resolution of the disease. This development means not only cure but also natural immunological prevention against new exposures to the virus.

The vaccine, prepared from the serum of hepatitis B carriers and having only surface antigen (HBsAg) with no Dane particles, will provide the formation of anti-HBs and this surface antibody protects against the disease. Although subtypes of virus B have been described, cross protection was also demonstrated after vaccination [13].

Based on these facts, simultaneous occurrence of HBsAg and anti-HBs should never happen. Nevertheless this concomitance has been reported [1,3,5,10,14,15]. In the earlier reports [5,10] five cases out of seven were blood-donors apparently healthy while the other two were sick patients; one in hemodialysis and the other with chronic active hepatitis. These Authors subtyped both anti-HBs and HBsAg pointing out that the paradoxal combination involved the d/y system of determinants. At that time they formulated two hypothesis trying to explain these findings. In the first one, a infection with one subtype develops a tolerant carrier state which is followed by another infection with a different subtype eliciting an immune response. In the second one, a vertical transmission in early life could lead to a tolerance to HBsAg of a particular subtype and a re-infection by another subtype would develop immunological reaction with the appearance of anti-HBs. In Foutch's series [3] the antibody has never appeared before the antigen. Although clinical data about all the patients are not available in these laboratory investigations, it was



shown that seven of the 13 patients had renal diseases, six of whom in hemodialysis. TABOR [14] describes a chronic HBsAg carrier and a Kaposi's sarcoma among his three patients and the reported case of BALAQUÉ [1] had a multisystemic disease. Besides the conclusion that anti-HBs can co-exist with HBsAg, these reports support the possibility of an atypical immunological response to hepatitis B virus, with monotypic anti-HBs failing to protect

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TABLE II

Case-reports of health-care workers Anti-HBs positive who posteriorly developed acute B hepatitis

Case report / Data	1	2	3	4
Authors	KOZIOL, D. E. et al.	SHERERTA, R. J. & HOOFNAGLE, J. H.	LINNEMANN, C. C. & ASKEY, P. A.	STRAUSS, E. et al.
Reference	J. Imunol. 117: 2260	N. Engl. J. Med. 309: 1519	Lancet 11: 346	
Year	1976	1983	1984	1984
Sex and age of patients	Male / 51	Female / 38	Female / —	Female / 40
Profession	Dentist	Nurse	Phlebotomist	Physician
Previous Anti-HBs Anti-HBc	+ / —	+ / —	+ / —	+ / not done
Method used	Passive hemaglutination	RIA	RIA	RIA
Type/time of contamination	Serum of hepatitis 6 months earlier	Needle-puncture 2 months earlier	Needle-puncture 4 months earlier	Needle-puncture 3 months earlier
Anti-HBs at the onset of hepatitis	Present	Present	Absent	Present*
Values of ALT	1198 u/l	2570 u/l	—	1052 u/l
Values of total bilirubin	24 mg%	8,8 mg%	—	20,5 mg%
Outcome	Complete recovery	—	—	Complete recovery
Hypothesis	Different sub-types of Anti-HBs	Anti-HBs blocked only by dithiothreitol	Inespecific IgM Anti-HBs	* Negative when re-tested by ELISA

against infection by a different subtype. If this happens only in persons with peculiar immunological responses, suffering from renal or other diseases is still to be demonstrated.

A different situation is herein reported. In this case report, as in three others of the literature [4,6,11], the antibody and not the antigen was detected from eight months to three years before the exposition to hepatitis B virus had occurred. Although aware of the risk of acquiring hepatitis by needle stick, the three hospital personnels did not take preventive measures believing that the anti-HBs in their serum indicated that they were immune against B hepatitis. Table II summarizes the main data from the three cases reported and includes the one herein described as the fourth.

The first case-report [4] was published in 1976, still using passive hemagglutination for the detection of anti HBs. No effect on anti-y reagent was demonstrated when the 8 categories of this antibody were subtyped in the serum taken before the acute B infection. This anti-y reaction appeared in the serum after clinical hepatitis. The two other cases were mentioned in letters to the editors while discussing screening before vaccination for B hepatitis. They are more recent cases and anti-HBs determinations were made by RIA. As a common feature, these two cases and the first one were negative for anti-HBc (the core antibody of B hepatitis). In the case-report of SHERERTZ & HOOFNAGLE [11] the anti-HBs was not blocked by any of the eight known subtypes of HBsAg but only by dithiothreitol, while LINNEMANN & ASKEY [6] suggested that the anti-HBs of their case was probably IgM.

Low-titre of anti-HBs, defined as a ratio less than 10 times the cutt-off when radioimmunoassay is used, could account for false-positive reactions. Nevertheless, high titre Anti-HBs

were observed in the third case-report proving that titring alone is not safe.

In this case-report, before determining subtypes, it was decided to re-test the serum samples for anti-HBs by another sensitive method, ELISA, and surprisingly the result was negative. Such fact would support two possibilities: a) the positivity by RIA was a false-positive reaction; b) the negativity by ELISA was due to less sensibility of this method. Studies from the literature [9] are not in favor of this second hypothesis, showing equal sensibility for RIA and ELISA.

Finally we should say that, although rare, false-positive anti-HBs or monotypic non-protective anti-HBs have been described when screening before hepatitis B vaccination. The policy of screening only for anti-HBs, in order to consider people from high risk groups as immune, should be seriously questioned. Associated positivity of anti-HBc seems to indicate real immunity and is easier to be performed than the "specificity testing" for anti-HBs, as proposed by FIEDLER [2]. The determination of the three markers (anti-HBs, anti-HBc and HBsAg) besides being more expensive, can be refused by some physicians and healthy-care workers. A practical alternative is not to screen at all, even with the possibility of administrating the vaccine to some immune persons and to assymptomatic carriers. But this policy is also expensive and cost effectiviness should be calculated, since we still have a blood-borne first generation vaccine. We hope technological advances in the near future will permit low-cost and free-risk vaccinations for B virus hepatitis.

RESUMO

Hepatite aguda B em paciente previamente positiva para o anticorpo de superfície (anti-HBs) determinado por radioimunoensaio. Relato de caso e revisão da literatura

A determinação do anticorpo de superfície contra a hepatite B (anti-HBs) precedendo a vacinação tem sido aconselhada com o intuito de encontrar indivíduos já imunes, para os quais esta administração seria desnecessária.

Um caso clínico é aqui apresentado, juntamente com a revisão de três casos mencionados na literatura, nos quais o anti-HBs foi positivo em pessoal hospitalar, o que justificou sua não vacinação e ausência de medidas preventivas face contaminação pelo vírus B. Malgrado esta aparente proteção pela presença do anti-HBs eles desenvolveram hepatite aguda típica pelo vírus B.

No primeiro caso da literatura a subtipagem revelou que o anti-HBs do passado e a infecção atual tinham determinantes d/y diferentes. Entretanto, os outros casos relatados mostravam ser o anti-HBs, dosado por radioimunoensaio (RIE), um falso positivo. Em nosso relato de caso o soro colhido no início da hepatite aguda foi re-testado por dois métodos diferentes e igualmente sensíveis. Observou-se persistência de positividade pelo RIE porém negatividade pelo enzimaimunoensaio (ELISA)

A determinação concomitante de anti-HBs e anti-HBc ou ainda dos três marcadores é uma das alternativas propostas, enquanto que outra conduta seria a não realização de qualquer teste pré-vacinação. Acreditamos que o desenvolvimento tecnológico propiciará produção de vacinas menos dispendiosas e totalmente isentas de risco em futuro próximo.

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