The frequency of hepatitis A and B viruses as the offending viral type in suspected hepatitis

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Summary

Three hundred and thirty blood samples from patients suspected of having hepatitis on clinical grounds but in whom the aetiology of the hepatitis was unknown (93 Whites and 237 Blacks) were tested for the presence of hepatitis B surface antigen (HBsAg), anti-HBs, total anti-hepatitis A virus (HAV) activity and anti-HAV of the IgM class. These tests identified the offending hepatitis virus whenever this was type A or type B, and also revealed the patient's immune status in respect of these viruses.

Among the White patients HAV was the cause of 32,2% of the cases of hepatitis and was found commonly in patients up to the age of 35 years, with 1 further example being identified among the patients over the age of 50 years. In contrast, among the Black patients this infection was found only in children, with none of the patients over the age of 5 years remaining susceptible to the disease.

Hepatitis B virus (HBV) was found frequently in Blacks of all ages and caused 39,7% of the cases of hepatitis, but was far less common among the Whites, in whom it was responsible for only 10,7% of cases. Serological evidence of exposure to HBV in the combined forms of HBsAg and anti-HBs reached 85,7% in Blacks aged between 36 and 50 years, while the highest level to be found in Whites was 45,5%, in the same age group.

Active hepatitis A or B infections were diagnosed in 43% of the White patients and 50% of the Black patients in the study.

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There is a wide variety of causes of hepatitis, some of which are infectious and others which are not, and many of these diverse agents result in symptoms which are very similar, often making it difficult to distinguish drug-induced hepatitis due, for example, to halothane or isoniazid from hepatitis which is of viral origin.[1] The fact that viral hepatitis itself may be caused by two distinct viral types has been recognized for many years, the two infections being differentiated initially on the basis of their varying incubation periods and modes of transmission. What has subsequently come to be called hepatitis B was known to have the longer incubation period (6 - 26 weeks) and was associated with a parenteral route of transmission, while hepatitis A had the shorter incubation period (2 - 6 weeks) and was transmitted largely via the oral-faecal route.

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Clinically the patient with hepatitis usually presents with malaise, fever, anorexia, pain in the right upper quadrant and jaundice;[1] the severity of the disease ranges from inapparent infections through the anicteric and acute, icteric forms to fulminant hepatitis, with some patients progressing to chronic liver disease.[2] This clinical picture may be so similar in the two types of viral hepatitis that differentiation on clinical grounds is rendered virtually impossible.[1] It is important to identify the offending viral type whenever possible because the prognosis, rates and modes of transmission differ greatly with the different viruses.[1] Equally important in this regard is the fact that there is no cross-immunity between the two infections and that prophylactic treatment of contacts of patients is often via the administration of two different immune globulin preparations.

The discovery of the Australia antigen in 1965 and its later association with the hepatitis B virus (HBV),[3] together with the demonstration of the hepatitis A virus (HAV) in the faeces of infected individuals during 1973,[4] pioneered a breakthrough in the understanding of the natural history of the two diseases and paved the way for accurate serological diagnosis and differentiation between the two types. The widespread use of the newly developed specific assays for the type A and type B viral strains in more recent years has revealed the presence of another serologically unrelated form of viral hepatitis which is currently ill-defined and bears the non-committal name of non-A, non-B hepatitis. The characteristic timing of the appearance in the plasma of the various virus-related antigens and antibodies during the course of hepatitis A and hepatitis B is summarized below.

Hepatitis A

Following an interval of 5 - 10 days from the time of primary exposure to HAV, virus is excreted in the faeces. The bulk of this excretion generally takes place in advance of the initial rise in plasma aminotransferase levels, and a significant proportion of patients do not exhibit virucopria during the acute phase. The assay of acute-phase stool samples for the presence of HAV is not, therefore, a suitably reliable method of diagnosing hepatitis A.[5] The infection does, however, result in the early production of a specific antibody, anti-HAV, which increases rapidly in titre. This early antibody is mainly of the IgM class, whereas the antibody found in convalescence is of the IgG class, and the method of choice for the diagnosis of this disease is the detection of specific anti-HAV of the IgM class in a serum sample taken during the acute phase of illness.[6] An alternative method would be to demonstrate a rising anti-HAV titre during the course of the disease,[1] but this causes a delay of 14 - 21 days in arriving at the diagnosis and is generally less satisfactory. The presence in the serum of anti-HAV which is exclusively of the IgG class may be taken as evidence of exposure to HAV at some time in the past and also as an indication of active immunity to a repeat infection.[7]

Hepatitis B

Infection with HBV is characterized by the appearance in the plasma of a virus-related antigen, hepatitis B surface antigen (HBsAg), approximately 4 - 12 weeks after primary exposure and

2 - 8 weeks before the onset of jaundice or any biochemical evidence of liver damage. HBsAg persists for the duration of the acute illness and its presence is therefore indicative of an active HBV infection. Following the clearance of the virus during convalescence HBsAg is no longer found in the circulation and its disappearance is usually followed, after an interval ranging from several weeks to several months, by the appearance of anti-HBs.[8] The appearance of this antibody indicates recovery from HBV infection, and it provides immunity to further infection by this particular virus type.[1] The presence or absence in the plasma of various other HBV markers such as hepatitis B e antigen (HBeAg), DNA-polymerase, anti-HBe and anti-hepatitis B core antigen (anti-HBc) may be useful indicators of the degree of infectivity of the patient and the stage of the infection, but this knowledge is not usually essential to the identification of the offending viral type.

Tests for selected HBV and HAV antigens and antibodies may be carried out on a patient with suspected hepatitis and the results assembled to provide a serological profile designed to aid in the differential diagnosis of the disease and giving an indication of the patient's immune status in respect of these viruses.

Patients and methods

Three hundred and thirty serum specimens from patients in the Eastern Cape and the Republic of Transkei who were suspected, on clinical grounds, of having hepatitis were included in this study, which was conducted between April 1980 and August 1981. In each case the provisional diagnosis was made by the patient's own clinician using his or her own parameters and no attempt was made on our part to standardize these criteria. The sample consisted of 93 Whites and 237 Blacks, with all children under the age of 1 year being excluded from the survey because of the known maternofetal transmission of some of the markers which were to be evaluated. Perusal of blood bank records and questioning of the clinician, where possible, established that none of the patients were likely to have received immune globulin or plasma infusion within the 90 days prior to being tested, a procedure which could also have been responsible for the passive transfer of antibodies.

Serum samples were screened for HBsAg and anti-HBs by solid-phase radio-immunoassay using commercially available reagents (Ausria II and Ausab respectively, both from Abbott Laboratories, North Chicago, USA). Total anti-HAV activity was also determined by radio-immunoassay (Havab, Abbott), as was anti-HAV activity of the IgM immunoglobulin class (Havab-M, Abbott). All assays were performed and the results interpreted in accordance with the manufacturer's instructions. The presence of IgG anti-HAV activity was inferred by a positive test for total HAV and a negative test for specific IgM anti-HAV activity.

Results

The frequency with which HBsAg was found in the 330 patients is shown in Table I, with the subjects categorized according to race group and age. Active hepatitis B was seen in Blacks of all age groups, with the highest prevalence in the 6 - 20-year-olds; above this age the marker became steadily less frequent. Unfortunately no samples were submitted from White children between the ages of 1 and 5 years, and the overall pattern in this race group is not quite so clear cut. No hepatitis B was found in the 13 patients aged between 6 and 20 years, and the percentages in the other three groups ranged between 8 and 18.

The prevalence of anti-HBs is shown in Table II, with the subjects categorized as before. Among the Black patients this antibody was seen to increase in frequency with age, ranging from 8,2% in the 1 - 5-year-olds to 63,1% in patients over the age of 50. In Whites the frequency with which the antibody was encountered increased from 7,7% in the 6 - 20-year-olds to 27,3% in those aged 36 - 50, but dropped to 8,3% in patients aged over 50 years. When the prevalences of HBsAg and anti-HBs are combined to reflect the overall HBV experience of this selected group of patients, the results shown in Table III, it is found that

TABLE I. PREVALENCE OF HBsAg IN PATIENTS WITH SUSPECTED HEPATITIS

Age group (yrs)	Whites			Blacks		
		HBsAg-reactive			HBsAg-reactive	
	No. tested	No.	%	No. tested	No.	%
1 - 5	0		—	49	14	28,6
6 - 20	13		0	63	36	57,1
21 - 35	57	7	12,3	59	29	49,2
36 - 50	11	2	18,2	28	10	35,7
> 50	12	1	8,3	38	5	13,2
Total	93	10	10,7	237	94	39,7

TABLE II. PREVALENCE OF ANTI-HBs IN PATIENTS WITH SUSPECTED HEPATITIS

Age group (yrs)	Whites			Blacks		
		Anti-HBs-reactive			Anti-HBs-reactive	
	No. tested	No.	%	No. tested	No.	%
1 - 5	0		—	49	4	8,2
6 - 20	13	1	7,7	63	13	20,6
21 - 35	57	7	12,3	59	18	30,5
36 - 50	11	3	27,3	28	14	50,0
> 50	12	1	8,3	38	24	63,1
Total	93	12	12,9	237	73	30,8

TABLE III. COMBINED PREVALENCE OF HBsAg AND ANTI-HBs IN PATIENTS WITH SUSPECTED HEPATITIS

Age group (yrs)	Whites			Blacks		
	No. tested	HBsAg or anti-HBs-reactive No.	%	No. tested	HBsAg or anti-HBs-reactive No.	%
1 - 5	0		—	49	18	36,7
6 - 20	13	1	7,7	63	49	77,8
21 - 35	57	14	24,6	59	47	79,7
36 - 50	11	5	45,5	28	24	85,7
> 50	12	2	16,7	38	29	76,3
Total	93	22	23,7	237	167	70,5

in both the Blacks and the Whites the prevalence reaches its maximum in the 36 - 50-year age group and that the frequency of the two markers is 85,7% among Black patients in this age group compared with 45,5% among the White patients. Over the age of 50 the frequency of the markers decreases in both groups, influenced by the fall in the prevalence of HBsAg among the Blacks and the decreasing prevalence of both anti-HBs and HBsAg among the Whites.

Table IV shows the prevalence of active hepatitis A as demonstrated by the presence of IgM anti-HAV, as well as the prevalence of immunity to this infection as reflected by the presence of IgG anti-HAV. Hepatitis A is seen to be very much a children's disease among the Blacks, with only a single patient, a girl aged 7 years, outside the group of patients age 1 - 5 years being found to have active hepatitis A. Of the other 187 Blacks investigated who were older than 5 years all were found to have IgG anti-HAV, and even in the 1 - 5-year group only 22% without serological evidence of HAV exposure were found. In the sample of 93 White patients the position was rather different, hepatitis A being common in the two categories covering patients aged between 6 and 35 years. One example was also found among the patients aged over 50 years. The level of immunity among the Whites was seen to increase with age, from 38,5% in the 6 - 20-year-olds to 91,7% in the patients aged over 50 years. Table V shows the prevalence of hepatitis A and B markers in the 330 samples investigated, with the patients grouped according to race and sex. Comparing the two White groups we found that there was a higher frequency of active hepatitis A among the females, which was balanced by a higher rate of immunity among the males, so that the overall HAV experience was almost identical. With respect to HBV infection in the White patients, a slightly higher prevalence of active disease and of overall experience was found among the males. HBsAg was found in an appreciably higher number of Black females than males, a difference which failed to reach statistical significance, and although the prevalence of anti-HBs was slightly higher in the males the overall HBV marker frequency remained higher in the females. The HAV exposure rate reached 100% in both sexes at an early

TABLE IV. PREVALENCE OF IgM AND IgG ANTI-HAV IN PATIENTS WITH SUSPECTED HEPATITIS

Age group (yrs)	Whites					Blacks				
		IgM anti-HAV		IgG anti-HAV			IgM anti-HAV		IgG anti-HAV	
	No. tested	No.	%	No.	%	No. tested	No.	%	No.	%
1 - 5	0		—		—	49	23	46,9	15	30,6
6 - 20	13	7	53,8	5	38,5	63	1	1,6	62	98,4
21 - 35	57	20	35,1	20	35,1	59		0	59	100
36 - 50	11	0	0	9	81,8	28		0	28	100
> 50	12	1	8,3	11	91,7	38		0	38	100
Total	93	28	30,1	45	48,4	237	24	10,1	202	85,2

TABLE V. PREVALENCE OF HEPATITIS A AND B MARKERS IN PATIENTS WITH SUSPECTED HEPATITIS DIVIDED ACCORDING TO RACE AND SEX

Race and sex	No. tested	HBsAg-reactive No.	%	Anti-HBs-reactive No.	%	IgM anti-HAV No.	%	IgG anti-HAV No.	%
White									
Females	45	4	8,9	6	13,3	17	37,8	20	44,4
Males	48	6	12,5	6	12,5	13	27,1	26	54,2
Black									
Females	102	46	45,1	28	27,4	9	8,8	88	86,3
Males	135	48	35,6	42	31,1	15	11,1	114	84,4

age, with slightly more active disease in the male children examined.

On the basis of HBsAg and anti-HAV IgM assays we were able to diagnose current hepatitis A or hepatitis B infections in 43% of the White patients and 50% of the Black patients who were examined.

Discussion

The 330 samples included in the present study were submitted at the discretion of the consulting physician, and in all probability the sample included many patients whose jaundice was induced by drugs or other non-viral hepatotoxins. For this reason no attempt has been made to use the results obtained to estimate the incidence of non-A, non-B hepatitis in this community, a diagnosis which at present is essentially one of exclusion, or the contribution of viral hepatitis generally to the overall picture.

Hepatitis B

In this study the presence of HBsAg was taken as being evidence of active HBV infection, and this infection was credited with being the cause of the current hepatitis. The fact that the patient may have been an asymptomatic carrier of HBsAg currently suffering from hepatitis due to some other agent was, of necessity, ignored, and this approach may have had a slight inflationary effect on the prevalence of active HBV disclosed in the analysis of the Black patients. The proportion of asymptomatic carriers among the White population is low enough to be insignificant in this regard.

Active hepatitis B was found in Blacks of all age groups, but was not found in the 13 Whites tested who were under 20 years of age. In each of the age groups investigated HBsAg was found with far greater frequency in the Black patients, accounting for only 10,7% of the hepatitis in Whites as a whole and for 39,7% of that in Blacks. The prevalence of anti-HBs in these two population groups further emphasized the greater rate of exposure in the Black group, with the antibody being encountered almost two and a half times as often. The steadily increasing prevalence of anti-HBs with advancing age is probably a reflection of the constant risk of exposure in all age groups rather than an indication of a decreasing frequency of infection in more recent years due to improvements in hygiene and general socio-economic conditions. The active disease which was found in all age groups seems to bear witness to this.

The higher prevalence of HBsAg in Black females than in Black males (Table V) is not statistically significant but is an interesting contrast to our findings in asymptomatic Black blood donors drawn from the same area and ethnic group as the patients, among whom 8,58% of males and 4,04% of females were found to be HBsAg-reactive (unpublished observations). Several previous studies (see references listed by Cossart[9]) have also consistently shown that the carrier rate is higher in men than it is in women in the same community, possibly owing to a preferential antigen peristence in males,[10] although there seems to be little difference in the incidence of acute hepatitis B when both sexes are at equal risk of exposure.[10]

Combining the results obtained with the HBsAg and anti-HBs assays reveals that the Black patients in this selected group have serological evidence of exposure to HBV three times as often as their White counterparts, with a peak level of 85,7% being found in the 36 - 50-year age group. The highest level seen in the Whites was in the same age group, the frequency being 45,5%.

Hepatitis A

Among the Black patients the likelihood of an individual contracting hepatitis A was found to be closely related to his or her age, with 46,9% of those under the age of 5 years being shown to have an active infection. In contrast, examination of the serum from 188 individuals over the age of 5 revealed only 1, a girl aged 7, who had hepatitis A at the time the sample was drawn, and failed to identify any person who remained susceptible to the infection. All were found to have anti-HAV of the IgG type. The rate of exposure to the virus in this ethnic group appears to be high enough to ensure that hepatitis A, either clinical or subclinical, remains an infection of early childhood only. This is in contrast to the findings of Villarejos[11] in Costa Rica where, in spite of the highly endemic environment, all infections were not acquired at an early age and immunity was far from universal in adults. In the examination of serum samples from 300 asymptomatic blood donors from the same population as the patients in the present study we failed to find any individual who lacked anti-HAV when tested by radio-immunoassay (unpublished observations). This is in keeping with the limited study of Frösner,[12] who failed to find a South African Black over the age of 10 whose serum did not contain anti-HAV.

Investigation of the samples taken from the 93 White patients revealed that in this group the picture was very different, with hepatitis A infection being found relatively commonly in children, adolescents and also adults. No serum samples were available from children between the ages of 1 and 5, although the 38,5% prevalence of IgG antibody found in the 6 - 20-year age group is an indication that exposure to HAV is fairly common from an early age; it is nothing like as common as it is in the Black community, however, leaving a reservoir of susceptible adults and adolescents who continue to contract the disease. This is essentially the pattern in most European countries.[12]

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