HEPATITIS B VIRUS: A PUBLIC HEALTH PROBLEM IN VENEZUELA[1]

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A workshop held in Caracas, Venezuela, on 13-14 May 1983 sought to review the information available about levels of hepatitis B virus infection in that country. This article provides a brief overview of the information presented at that meeting.

Introduction

Hepatitis induced by the hepatitis B virus (HBV) constitutes a significant public health problem around the world. The importance of the infection's epidemiology arises chiefly from the different developmental phases of the disease (acute and chronic) and from the existence of carriers who show no clinical or biochemical evidence of hepatic disease, but who carry hepatitis B surface antigen in their serum. These carriers are able to transmit the disease agent and are also susceptible to liver disease at some point in their lives *(1)*.

A recent report pointing to the existence of about two hundred million carriers of the HB virus surface antigen in diverse parts of the world is pertinent in this context *(2)*. Particularly high carrier prevalences have been observed in Africa and East Asia. Such prevalences tend to vary a good deal in the Americas, ranging from very high in certain Caribbean island countries such as the Dominican Republic to relatively low in various South American countries such as Chile *(3, 4)*.

Regarding Venezuela, one study that dealt with voluntary blood donors in the western portion of Caracas found 2.8% of the donors tested to be positive for hepatitis B surface antigen *(3)*. Also, an increase in the number of clinical hepatitis cases has been reported by the health ministry's Public Health Administration in recent years, and high levels of endemicity have been detected among groups of Venezuelan Indians *(5, 6, 7)*.

Responding to these findings, in 1983 the

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Public Health Administration directed the National Reference Center for Clinical Immunology (CNRIC), site of the WHO Collaborating Center for Clinical Immunology (CECOIC) in Venezuela, to organize a workshop for the purpose of discussing three basic subjects relating to hepatitis B virus (HBV) in Venezuela. These subjects were (1) the immunoepidemiology of HBV in Venezuela; (2) the clinical-morphologic spectrum of the disease in Venezuela; and (3) the national vaccination program. This article summarizes the proceedings and conclusions of that workshop, which was held in Caracas on 13 and 14 May 1983. Particular attention is given to immunoepidemiologic studies carried out by CNRIC/CECOIC, the findings of which have been used as a reference in establishing policies for the prevention of hepatitis B in Venezuela.

Immunoepidemiology

HBV in Western Indian Populations

Between 1979 and 1981, an epidemic of hepatitis occurred among the Yucpa Indians of Zulia State. The disease typically followed a severe acute course of short duration, rapidly became chronic, and produced significant mortality. Studies seeking the specific causal agent of the severe clinical pictures involved were able to confirm that there was a high prevalence of HBV carriers possessing markers for the Delta viral agent *(6, 7, 9)*.

The Yucpa are a population of some 5,000 Indians of Carib extraction living in 21 communities in the Perijá Mountain Range in western Zulia State on the Venezuelan-Colombian border. Among other things, many Yucpas were found to have severe scabies with open skin lesions, a circumstance that could conceivably have contributed to the persistence of the B virus infection.

Overall, during the three-year 1979-1981 period, 149 cases of viral hepatitis are known to have occurred among the Yucpa; these resulted in 34 deaths and at least 22 cases of chronic hepatitis. High HBV endemicity was observed, together with evidence of superinfection by the Delta viral agent in 84% of the HBsAg-positive cases *(5)*.

At the pilot unit of CNRIC/CECOIC in Caracas, we used radioimmunoassay (RIA) testing[10] to study 20 serum specimens provided by physician-epidemiologists in the affected area. These specimens had been taken from 20 Yucpa Indians in the community who belonged to families with a history of hepatitis B. As Table 1 shows, 13 (65%) of these specimens tested positively for HBsAg, 10 (50%) were positive for antibody to hepatitis B virus surface antigen (anti-HBs), and 19 (95%) were strongly positive for antibody to hepatitis B virus core antigen (anti-HBc).

For purposes of comparison, 25 serum specimens obtained at random from a different Indian population were examined. These specimens, provided by physicians of the Amazon Center for the Investigation and Control of Tropical Diseases (Ministry of Health and Social Welfare), were obtained from members of a Yanomami Indian community located in the Parima Mountain Range in the Federal Territory of Amazonas in southern Venezuela near the Brazilian border. (The Amerindian Yanomami, unlike the Yucpa, are not of Carib extraction.) Examination of these 25 sera showed a high prevalence of antibodies to HBV surface and core antigens (in 80% and 84% of the specimens, respectively), but a relatively low prevalence of HBsAg, which was detected in only one serum (see Table 1).

Survey Data from Other Populations

Besides investigating HBV in Indian populations, CNRIC/CECOIC has begun an immunoepidemiologic survey to determine the prevalence of HBV serologic markers in cross-sections of the population at low risk of infection in the Caracas Metropolitan Area and in zones in the interior of the country. As of this writing, 662 serum specimens from this general popula-

[10]These tests were performed with kits obtained from the Diagnostic Division of Abbott Laboratories in Caracas.

Table 1. Prevalence of HBV serologic markers among groups at high, intermediate, and low levels of risk.

Risk level	Serologic markers											
	HBsAg			Anti-HBs			Anti-HBc			HBeAg		
	No. tested	No. positive	(% positive)	No. tested	No. positive	(% positive)	No. tested	No. positive	(% positive)	No. tested	No. positive	(% positive)
Low risk[a,b]	662	9	(1.3)	662	87	(13.1)	662	60	(9.0)	–	–	–
Intermediate risk	87	5	(5.7)	74	9	(12.1)	80	15	(18.7)	–	–	–
High risk:												
Indian groups:												
Yucpa Indians	*20*	*13*	*(65)*	*20*	*10*	*(50)*	*20*	*19*	*(95)*	*10*	*2*	*(20)*
Yanomami Indians	*25*	*1*	*(4)*	*25*	*20*	*(80)*	*25*	*21*	*(84)*	*1*	*0*	*(0)*
Patients undergoing immunodiagnosis[c]	485	112	(23.0)	424	85	(20.4)	430	227	(52.7)	112	14	(12.5)

[a]A total of 112 sera (16.9%) tested positively for one or more markers.
[b]In all, 195 of the 662 sera were obtained from "adolescents" (subjects 12 to 19 years old, the average age being 16): none of these sera was positive for HBsAg, but 18 (9.2%) were positive for one or more of the other serologic markers.
[c]A total of 128 specimens testing negatively for HBsAg tested positively for one of the other markers.

Table 2. Geographic distribution of the 662 low-risk subjects.

Regional distribution	Serologic markers								
	HBsAg			Anti-HBs			Anti-HBc		
	No. tested	No. positive	(% positive)	No. tested	No. positive	(% positive)	No. tested	No. positive	(% positive)
Western Region	197	1	(0.5)	197	21	(10.6)	197	22	(11.1)
Central Region	170	1	(0.6)	170	34	(20.0)	170	19	(11.1)
Federal District:									
Eastern metropolitan area (Petare)[a]	*100*	*7*	*(7)*	*100*	*17*	*(17)*	*100*	*13*	*(13)*
Other portions of the district	*195*	*0*	*(0)*	*195*	*11*	*(7.1)*	*195*	*6*	*(3.0)*

[a]A total of 25 sera (25%) tested positively for one or more markers.

tion have been subjected to RIA testing. These samples were obtained from apparently healthy individuals chosen in accordance with a protocol devised by the Center for Biological Studies on Growth and Development of the Venezuelan Population *(10)*. In addition, 87 sera obtained from the medical and paramedical personnel of our laboratory (both temporary and permanent staff members) were integrated into the study as representing a population at intermediate risk of infection with HBV *(11)*. Finally, 485 samples were included that came from subjects with liver disease who were undergoing clinical immunodiagnosis.

As Table 1 shows, only 1.3% of the 662 specimens from the low-risk population of apparently healthy subjects tested positively for HBsAg, as compared to 5.7% of the 87 samples from the intermediate-risk group. However, it is important to note that varying percentages of antibodies to HBsAg were detected in all the population cross-sections studied (see Tables 1 and 2), a finding that points to a significant prevalence of acquired immunity. In this same vein, 195 of the 662 sera were obtained from "adolescent" subjects 12-19 years old. None of the sera tested positively for HBsAg, but 18 (9.2%) tested positively for one or more of the other markers.

Regarding the laboratory personnel and liver disease patients, it is interesting that the laboratory personnel showed a higher prevalence of antibody to core antigen (anti-HBc) than of antibody to surface antigen (anti-HBs). Of the 485 patients undergoing immunodiagnosis, 112 yielded sera positive for surface antigen and 12.5% of these 112 were found positive for HBeAg. Also, 50% of those liver disease patients whose sera tested negatively for HBsAg were found positive for anti-HBc.

In general, the data acquired as of 1983 indicate that Venezuela's population is epidemiologically diverse with regard to HBV, the virus being highly endemic among certain groups (such as the Yucpa Indians), moderately endemic among the tested group of medical and paramedical laboratory workers, and of low endemicity among apparently healthy members of the general population. Within this latter group the highest prevalences of HBV serologic markers nd to be found among residents of marginal areas. The general apparent prevalences of HBsAg and other markers in the Venezuelan population, as indicated by our work as of 1983, together with reported prevalences in seven other countries *(2, 4, 11, 12, 13)*, are shown in Table 3.

Table 3. Prevalences of HBV as indicated by the results of serologic studies in Venezuela and seven other countries or regions.

	% sera positive for:	
	HBsAg	Any marker (HBsAg, HBeAg, Anti-HBs, Anti-HBc)
United States *(8)*	0.3	3-5
Chile *(4)*	0.3	6.7
Venezuela	1.3	16.9
Great Britain *(11)*	0.1-0.2	
Greece *(11)*	3	
Italy (southern) *(11)*	3	
Africa *(11)*	15	
Saudi Arabia *(12)*	10	±30

The Clinical-Morphologic Spectrum of HBV Infection in Venezuela

As was reported during the workshop, a clinical follow-up study was made of 108 acute viral hepatitis cases with positive serologic markers for HBV. The patients involved were seen at urban hospitals in the Caracas area and in the state of Lara. The results of the study indicated that a preponderance of the subjects with acute HBV infections were in their twenties and thirties. There was no marked predominance of males or females among the study subjects. Clinical-biochemical symptoms (including elevated levels of transaminases and bilirubin) lasted for eight to 12 weeks. The dominant clinical symptom was cholestasis.

Persistence of the surface antigen was observed in only seven patients; in the remaining

patients, tests for antigenemia became negative within six months of their initial illness. Morphologically, the observations reported suggest that cases of intensely active chronic hepatitis caused by HBV are the exception in Venezuela. Also, hepatocytes with "ground-glass" protoplasm indicating the presence of surface antigen are seen less frequently, both in carriers and in other infected subjects, than in countries where the prevalence of HBsAg carriers is higher (see Table 3). However, it has not yet been possible to explain these differences, which indicates a need for a properly controlled comparative study.

Vaccination against HBV

The cost-effectiveness and cost-benefit ratios of such projects as the National Hepatitis B Vaccination Program to prevent transmission of hepatitis B virus must depend to a great extent on the value of the immunoserologic tests performed and the current cost of the vaccine *(11, 14)*. (Partly because this vaccine must be imported, it is not accessible to all communities.) Also, the survey results available at present indicate that the main transmission route—and hence the route most in need of interruption—is from one adult to another.

Conclusions

The studies reported here indicate that the prevalence of HBsAg in Venezuela generally is around 1.3% in apparently healthy subjects, while the overall prevalence of one or more of the HBV markers in apparently healthy subjects is in the range of 16.9%. The evidence available also indicates that the outcome of acute HBV infection is frequently favorable in Venezuela. Finally, data from the survey to detect HBV markers in various Venezuelan populations show that vaccination against HBV is indicated in this country for groups at high and intermediate risk against the virus. However, it was also emphasized at the workshop that there was no indication whatever justifying large-scale vaccination or indiscriminate vaccination of the population at large.

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SUMMARY

On 13 and 14 May 1983 Venezuela's National Reference Center for Clinical Immunology (CNRIC) sponsored a workshop on the hepatitis B virus (HBV) problem in Venezuela. Major topics covered included the immunoepidemiology of HBV in Venezuela, the clinical-morphologic spectrum of the disease, and Venezuela's national vaccination program. This article summarizes the findings reported at the workshop.

including various findings of a major survey conducted by CNRIC.

Overall, available information suggests that while relatively high prevalences of hepatitis B surface antigen (HBsAg) and other viral markers are found among certain high-risk groups (including certain Indian populations) and intermediate-risk groups (such as medical laboratory workers), the prevalence of HBsAg among apparently healthy members of the general Venezuelan population is around 1.3%, while the overall prevalence of HBV serologic markers is in the range of 16.9%. In general, the outcome of acute HBV infections in Venezuela has tended to be favorable; and while there is justification for vaccinating high-risk and intermediate-risk groups against the virus, there is no evidence justifying large-scale or indiscriminate vaccination of the public at large.

REFERENCES

(1) Robinson, W. S. Biology of Human Hepatitis Viruses. In: D. Zakin and T. D. Boyer (eds.). *Hepatology*. W. B. Saunders, Philadelphia, 1982. pp. 863-910.

(2) McCollum, R. W., and A. J. Zuckerman. Viral hepatitis: Report on a WHO informal consultation. *J Med Virol* 8:1-29, 1981.

(3) Mazzur, S., N. Nath, C. Fang, M. J. Bastiaans, J.L.M. Molinaris, M. Balcaser, S. Beker, E. A. Brunings, A. R. Cameron, V. Farrell, O. H. Fay, G. Labrador-González, G. González, A. Gutiérrez, C. Jaramillo, R. Katz, M. B. Leme López, E. Levy-Koenig, H. Rodríguez-Moyado, R. A. de Torres, and M. Velasco. Distribution of hepatitis B virus (HBV) markers in blood donors of 13 Western Hemisphere countries: Proceedings of the Red Cross Latin American Hepatitis B Workshop. *Bull Pan Am Health Organ* 14(1):44-51, 1980.

(4) Velasco, M., M. González-Cerón, C. De La Fuente, A. Ruiz, S. Donoso, and R. Katz. Clinical and pathological study of asymptomatic HBsAg carriers in Chile. *Gut* 19:569-571, 1978.

(5) Organización Panamericana de la Salud. Hepatitis grave causada por el virus Delta en Venezuela. *Boletín Epidemiológico* 3:8, 1982.

(6) Krugman, S. The newly licensed hepatitis B vaccine: Characteristics and indications for use. *JAMA* 247:2012-2015, 1982.

(7) Rizzetto, M., M. G. Canese, S. Arico, O. Crivelli, C. Trepo, F. Bonino, and G. Vernme. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. *Gut* 18:997-1003, 1977.

(8) United States Centers for Disease Control. Inactivated hepatitis B virus vaccine. *Morbidity and Mortality Weekly Reports* 31:317-328, 1982.

(9) Francis, D. P. Selective health care: Strategies for control of disease in the developing world: III. Hepatitis B virus and its related diseases. *Reviews of Infectious Diseases* 5:322-329, 1983.

(10) Machado B., I. Inmunopatología e inmunodiagnóstico de la hepatitis viral inducida por virus B. In: N. E. Bianco and G. Torrigiani (eds.). *Inmunología clínica 83*. Ediciones de la Biblioteca, Universidad Central de Venezuela, 1983. pp. 431-444.

(11) Blackwell Scientific Publications. Viral Hepatitis. In S. Sherlock (ed.). *Diseases of the Liver and Biliary System*. London, 1981, pp. 244-269.

(12) Little, P. J. Hepatitis B vaccination. *Saudi Med J* 7:1-4, 1983.