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Human Leukocyte Antigen (HLA) in Patients with Idiopathic Portal Hypertension (IPH)

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SATOH, H., IWASAKI, Y., OHKUBO, A., BEPPU, T., FUTAGAWA, S., SUGIURA, M. and JUJI, T. *Human Leukocyte Antigen (HLA) in Patients with Idiopathic Portal Hypertension (IPH)*. Tohoku J. exp. Med., 1980, **131** (4), 393–397 —— Both cryptogenic liver cirrhosis and idiopathic portal hypertension without pathological findings of liver cirrhosis (IPH) are relatively common in Japan. To find difference between IPH and cryptogenic liver cirrhosis of Japanese, we investigated human leukocyte antigen (HLA), familial clustering of liver diseases as well as prevalence of HBs antigen in 31 patients with IPH. The age of patients with IPH ranged between 6 and 67 years old (mean, 40 years). The ratio of female to male in patients with IPH was 3.1. The incidence of chronic liver diseases in the relatives of patients with cryptogenic liver cirrhosis was significantly high (29.1%), whereas that in the relatives of patients with IPH was not high (12.9 %) as compared with hospitalized controls (8.9%). The phenotype frequencies of the specificities of HLA A and B loci in patients with IPH did not differ from those in healthy controls. And the incidence of HBs antigen and antibody in patients with IPH (3.2% and 20.7%, respectively) was similar to those in normal subjects in Japan. These findings suggest that IPH in Japan is a different clinical entity from cryptogenic liver cirrhosis and that HB virus may not be one of the main causes of IPH. ——— IPH; HLA; HBs antigen; cryptogenic liver cirrhosis

Both cryptogenic liver cirrhosis and idiopathic portal hypertension without pathological findings of liver cirrhosis (IPH) are relatively common in Japan (Matsushita 1975; Sugiura et al. 1977). Relationship between IPH and cryptogenic liver cirrhosis has been a quite controversial problem, especially in terms of pathogenesis and predisposition.

Recently, some investigators reported high incidence of HBs antigen in patients with IPH (Shikata et al. 1976; Yoshikawa 1978). On the other hand, susceptibility has been postulated to play a role in the development of cryptogenic liver cirrhosis, and association between cryptogenic liver cirrhosis of Japanese and major histocompatibility antigen (HLA) B5, Bw54 and DYT was reported by Ohkubo et al. (Ohkubo et al. 1977; Ohkubo 1979). To find difference between IPH and cryptogenic liver cirrhosis, we investigated HLA, familial clustering of liver disease and prevalence of HBs antigen in patients with IPH.

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Patients and Methods

Thirty-one unrelated patients with IPH and 174 healthy controls were typed for HLA specificities in A and B loci by microlymphocytetoxicity test (Terasaki and McClelland 1964). The diagnosis of IPH was made according to the criteria proposed by the Ministry of Health and Welfare Idiopathic Portal Hypertension Research Comittee, Japan (Sugiura et al. 1977). In 27 out of 31 cases, liver showed histologically minimum to moderate fibrosis, except 4 cases in which liver was macroscopically found almost normal and liver biopsy was not carried out. Clinical and laboratory findings in patients with IPH are summarized in Table 1. HBs antigen was detected by immunoadherence hemagglutination (IAHA) or reverse passive hemagglutination (RPHA), HBs antibody by passive hemagglutination (PHA). Standard techniques were used to measure liver function tests and to determine hematological values. Indocianine green (ICG) retention was expressed by the percentage of ICG at 15 min after a single intravenous injection. It was studied whether liver diseases were found in the relatives within the second degree of patients with IPH. Statistical analysis was done by chi square test with Yates' correction.

Table 1. *Clinical and laboratory findings in patients with idiopathic portal hypertension (IPH)*

	PVP* (mmH_2O)	Spleen (g)	Albumin (g/100 ml)	Bilirubin (mg/100 ml)	SGOT (K.U.)	ICG(15′) (%)	Platelet ($10^4/mm^3$)
IPH	333±20	850±76	3.7±0.1	1.0±0.1	24±1	12.6±1.8	8.0±0.8
Normal range	<120	70-130	4.0-5.0	0.3-1.2	8-28	10	14-40

* Portal venous pressure.
Data are preseted as mean±S.E.M.

Results

Fig. 1 shows the age and sex distribution of patients with IPH. The age of patients with IPH ranged between 6 and 67 years old. The ratio of female to male in patients with IPH was 3.1. This ratio was similar to the result obtained by a nation-wide epidemiological survey of IPH (Sugiura et al. 1977).

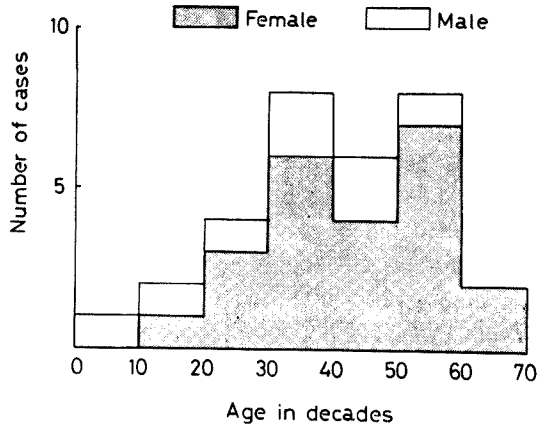

Fig. 1. The age and sex distribution of patients with idiopathic portal hypertension (IPH).

Table 2 shows the incidence of chronic liver diseases in the relatives of patients with IPH, those with cryptogenic liver cirrhosis and hospitalized controls without liver diseases. Hospitalized controls entered our hospital from Jan. to Dec. in 1978. The incidence of chronic liver diseases in the relatives of patients with cryptogenic liver cirrhosis was significantly high, whereas that in the relatives of patients with IPH was similar to hospitalized controls.

Table 3 shows the results of HLA typing of patients with IPH. The phenotype frequencies of the specificities of HLA A and B loci in patients with IPH did not differ from those in controls.

TABLE 2. *The incidence of chronic liver diseases in the relatives of patients*

Proband	Number of cases	Incidence (%)	
Idiopathic portal hypertension	31	12.9	n.s.
Cryptogenic liver cirrhosis	55	29.1	$p<0.01$
Diseases other than liver diseases	327	8.6	

n.s., not significant.

TABLE 3. *Comparison between patients with IPH and healthy controls with regard to the frequency of HLA phenotypes in the first (A) and the second (B) loci*

HLA	IPH (n=31) (%)	Control (n=174) (%)	χ^2
1st locus			
A1	0	1.1	
A2	35.4	38.5	
A3	0	1.7	
A9	61.3	58.0	
A10	25.8	20.7	
A11	19.8	17.2	
A19	3.2	4.0	
Aw 19	0	0	
Aw 30	3.2	10.3	
Aw 31	9.7	4.0	
Aw 33	0	2.9	
Aw 34			
2nd locus	41.9	39.7	
B5	3.2	13.8	
B7	9.7	16.7	
B12	3.2	2.3	
B13	22.6	17.8	
B15	19.4	5.7	5.01
Bw 16	3.2	1.1	
B17	0	0.6	
Bw 21	9.7	14.9	
Bw 37	0	0.6	
B40	51.6	35.1	
Bw 46	0	6.9	
Bw 48	6.5	3.4	
Bw 53	0	1.7	
Bw 54	22.6	12.6	

The incidence of HBs antigen and HBs antibody in patients with IPH was 3.2% and 20.7%, respectively. These are similar to those in normal subjects in Japan (2.7% and 18.4%, respectively) (Nishioka et al. 1975).

Discussion

As shown in Fig. 1, IPH was found predominantly in middle aged female. On the other hand, cryptogenic liver cirrhosis was reported to be prevalent among middle aged male. (Matsushita 1975).

The incidence of chronic liver diseases in the relatives of patients with cryptogenic liver cirrhosis was significantly high, whereas that in the relatives of patients with IPH was not high compared with controls.

As shown in Table 3, IPH was not associated with any of the HLA specificities in A and B loci. In contrast, cryptogenic liver cirrhosis was reported to be associated with HLA B5, Bw54 and DYT in Japanese (Ohkubo et al. 1977; Ohkubo 1979).

These findings altogether suggest that the two diseases, IPH and cryptogenic liver cirrhosis, may be different in terms of pathogen and/or susceptibility.

Recently, it was reported that HBs antigen was found by orcein stain frequently in liver tissues from patients with IPH (Shikata et al. 1976; Yoshikawa 1978). In our study, however, the incidence of HBs antigen or antibody in sera in patients with IPH was similar to that in normal subjects (Nishioka et al. 1975). This finding was compatible with the result obtained from a nation-wide survey of IPH (Sugiura et al. 1977). Therefore, it is difficult to conclude that HB virus is one of the main causes of IPH.

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References

1) Imanaga, H., Yamamoto, S. & Kuroyanagi, Y. (1962) Surgical treatment of portal hypertension according to state of intrahepatic circulation. *Ann. Surg.*, **155**, 42–50
2) Matsushita, H. (1975) Epidemiology of hepatic cirrhosis in Japan. In: *Hepatic Cirrhosis.* 1st ed., edited by T. Oda, Nankodo, Tokyo, pp. 15–26.
3) Nishioka, A., Levin, A.G. & Simons, M.J. (1975) Hepatitis B antigen, antigen subtypes, and hepatitis B antibody in normal subjects and patients with liver diseases. *Bull. World Hlth Organ.*, **52**, 293–300.
4) Ohkubo, A., Okimoto, K., Iwasaki, Y., Kosaka, K., Juji, T. & Toyama, H. (1977) Association of human leukocyte antigen (HLA)–B5 and Bw22-J with hepatic cirrhosis of apparently unknown etiology. *Tohoku J. exp. Med.*, **123**, 257–263.
5) Ohkubo, A. (1979) HLA associated factors contributing to the development of liver cirrhosis. *J. Jap. Soc. intern. Med.*, **68**, 1406–1410.
6) Shikata, T., Uzawa, T. & Yamazaki, S. (1976) Causalgenesis of liver fibrosis accompanied with portal hypertension. *Acta hepatol. jap.*, **17**, 417–424.

7) Sugiura, M. (Chairman) et al. (1977) *Annual Report of the Ministry of Health and Welfare Idiopathic Portal Hypertension Research Committee, Japan, 1976.*
8) Terasaki, P.I. & McClelland, J.D. (1964) Microdroplet assay of human serum cytotoxins. *Nature*, **204**, 998–1000.
9) Yoshikawa, K. (1978) Immunological studies in the etiology of idopathic portal hypertension. *J. Jap. Surg. Soc.*, **79**, 538–553.