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RHEUMATIC FEVER AND HEPATITIS B SURFACE ANTIGEN*

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Rheumatic fever is a common collagen tissue disease that generally begins in childhood and affects the heart, joints, skin and central nervous system. It is very important as it causes acute carditis and chronic heart disease. Although rheumatic fever has diminished in Western countries, it continues to be a problem in Turkey.

During a study of school-age children in the vicinity of Ankara, the frequency of rheumatic fever was established as 0.2%; the rate is only 0.05% in the United States. The fall in prevalence of the disease in the U.S. is attributed to improvement of socio-economic conditions and effective treatment of streptococcus[1,2]. Rheumatic carditis is still the leading form of acquired heart disease in children[2]. Rheumatic fever is considered by many to be secondary to a preceding streptococcal infection. However, one-third to one-half of the patients with rheumatic heart disease do not present a definite history of a preceding streptococcal infection[3].

Rheumatic fever is described pathogenically as a streptococcus-stimulated, immunopathological condition. However, it is still not clear why rheumatic fever occurs at a rate of 0.3% after streptococcal infection and 2-3% following streptococcal epidemics. Furthermore, it is also thought that as yet unidentified factors, and in particular viruses, may affect the occurrence of this immunopathological condition[4].

The role of hepatitis B antigen in certain collagen tissue diseases has been considered in recent years[5]. Preliminary studies on rheumatic fever were carried out, and the patients were found to have a higher frequency of HB_sAg than the controls[6, 7]. In the light of these findings, the present study was undertaken in which the sera of rheumatic fever patients were screened for antigen and antibody with the highly sensitive radioimmunoassay (RIA) method, and the deposition of HB_sAg in heart tissue was studied using an immunofluorescent technique.

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Material and Methods

This study was carried out on 177 serum samples from 157 children between 5 and 17 years of age, 46 of whom had active rheumatic heart disease, 51 rheumatic heart disease at the inactive stage, and 20 acute rheumatic arthritis without carditis; 40 were healthy controls.

The RIA method was used to screen for both HB_sAg and anti-HB_s in all sera. Abbott Laboratories' AUSRIA II-125 (hepatitis associated antibody ^{125}I human) was used to screen for antigen and AUSAB (hepatitis B surface antigen ^{125}I human "subtypes ad and ay") for antibody.

For the tissue studies, samples were taken either from the left auricle or from the left auricle and the mitral valve during surgery on 27 patients with chronic rheumatic heart disease. These tissues were frozen immediately and were cut in cryostat. Sections were stained by the direct immunofluorescent technique[8] for the presence of antigen-antibody complexes.

Fluorescein labelled anti-HB_s, anti-IgG, anti-IgM, anti-IgA and anti-complement C_3 (B_1C) sera prepared in rabbits were obtained from Behringwerke laboratories and used for tissue stainings.

Findings

HB_s antigen was found to be positive by RIA technique in 19.5% of the patients with active rheumatic heart disease, 11.7% of the patients with chronic rheumatic heart disease, 25% of the patients with rheumatic arthritis without carditis and 5% of the control group (Table I).

TABLE I

HB_s AND ANTI-HB_s IN PATIENTS WITH RHEUMATIC FEVER (RIA TECHNIQUE)

	HB_sAg			Anti-HB_s		
	No. of patients tested	Positive	%	No. of patients tested	Positive	%
Rheumatic heart disease (active) patients	46	9	19.5	46	12	26
Rheumatic heart disease (inactive) patients	51	6	11.7	50	16	32
Acute rheumatic arthritis without carditis	20	5	25	18	4	22.2
Controls	40	2	5	40	13	32.5

The screening for anti HB_s using the same technique in the same group of patients indicated positive results as follows: 26% of the active carditis patients, 32% of the chronic cases, 22% of the acute arthritis patients and 32.5% of the controls.

Statistical comparison in this study was by the chi-square method. The frequency of antigen encountered in the patients was found to differ significantly from that in the control groups. There was no statistically significant difference between the patients and controls for anti-HB_s frequency.

As outlined in Table II, immunofluorescent staining of heart tissue was obtained from 27 patients with chronic rheumatic heart disease, revealing deposits of both HB_sAg and complement in 8 of them (30%). IgM and IgA deposits were revealed in the heart tissue of 5 patients, 3 of whom also revealed accumulations of IgG. Serum was available for 5 of the 8 patients who disclosed HB_sAg in heart tissue. Only one of the five revealed a positive test for HB_sAg in serum.

TABLE II

RESULTS OF IMMUNOFLUORESCENT STAINING OF DEPOSITS IN THE HEART TISSUE OF 8 PATIENTS WITH CHRONIC RHEUMATIC CARDITIS

	Heart Tissue				
HB_sAg in serum	HB_sAg	IgG	IgM	IgA	$C_3(\beta_1C)$
Positive	+	−	−	−	+
Negative	+	−	+	+	+
	+	−	−	−	+
	+	+	+	+	+
	+	+	+	+	+
No serum could be obtained	+	+	+	+	+
	+	−	−	−	+
	+	−	+	+	+

Discussion

It is not known why rheumatic fever occurs after streptococcal infection in only 2% of the cases. It is thought that it may be due to the presence of an inducing factor.

Today, the value of Jones' criteria of a high ASO titer and a positive beta hemolytic streptococcus throat culture in the diagnosis of rheumatic fever is being debated[9].

Viral and bacterial infections can often occur concurrently. Experimental studies on animals have shown that bacterial infection compounded by viral infection has a

synergistic effect, very apparent in hemolytic streptococcus, pneumococcus and staphylococcus infections [10].

The total rate of positive HB_s antigens and anti-HB_s in active rheumatic carditis was 45.5% in the present study. This rate is indicative of a high frequency of contact with the hepatitis B virus. It is seen that the frequency of HB_s antigen is higher in patients with active rheumatic heart disease and those with acute rheumatic arthritis than in healthy people. The high frequency of HB_s antibodies in patients with rheumatic heart disease in the inactive stage is also worth noting. This gives the impression that there is a relation between the active stage of rheumatic fever and HB_s antigenemia.

There has been acceptance of the theory that if the cellular immune response of a patient is inadequate, he would be an apparently healthy carrier or an asymptomatic patient. It can also be considered that patients with HB_s antigenemia are able to impair cellular immune response [11]. It is also probable that patients with antigenemia give inadequate response to streptococcal infection, or that streptococcal infection is important in the activation of latent HB virus.

Extrahepatic localization of HB_s Ag has been shown. Antigen-antibody complexes accumulate in the skin, joints, small arteries, arterioles and renal glomeruli, causing disease. Polyarthritis, polyarthralgia, rash, subcutaneous nodules, vasculitis and glomerulonephritis related to these immune complexes develop [12-17].

Figure 1

Immunofluorescence with antiserum to HB_sAg is seen in the myocardial muscle fibers.

In this study, deposition of HB_sAg in association with complement C_3 was observed using the immunofluorescent technique in the subendocardial heart tissue (and slightly in the myocardial muscle fibers) of 8 patients (Figures 1-2). The deposition of G, M, A immunoglobulins was observed in certain of them (Table II). In the literature, there is no study of HB_sAg in rheumatic fever, but lesions resembling rheumatic heart lesions can be produced in animals with other viruses[4, 18-20].

The incidence of HB_sAg in the serum of rheumatic fever patients was found to be high, and the fact that the antigen in the heart tissue could be seen with the fluorescence leads to the belief that the HB virus has a role in the pathogenesis of rheumatic fever. Further study is necessary to clarify this subject.

Figure 2

Immunofluorescence to demonstrate C_3 in the subendocardial heart tissue and muscle fibers.

Summary

The hepatitis B antigen and antibody were sought in the serum of 117 patients with rheumatic fever and 40 healthy controls by the RIA technique. HB_s antigen was found to be positive in nine of the 46 patients (19.5%) with active rheumatic heart diseases, six of 51 patients (11.7%) with chronic rheumatic heart disease and five of the the 20 patients (25%) with acute rheumatic arthritis without carditis. Of the 40

healthy controls, only two (5%) were found to have positive hepatitis HB_s antigen in the serum. Anti HB_s was found to be positive in twelve of forty-six patients (26%) with active rheumatic heart disease, sixteen of fifty patients (32%) with chronic rheumatic heart disease, four of eighteen patients (22.2%) with acute rheumatic arthritis without carditis and thirteen of forty healthy controls (32.5%).

Statistical comparisons for HB_s antigen frequency between patients with rheumatic fever and healthy controls revealed a significant difference. However, there was no statistically significant difference between rheumatic fever patients and controls for anti HB_s frequency.

For the tissue studies, samples were taken from 27 chronic rheumatic valvular heart disease patients. In eight (29.9%) of these specimens, HB_s antigen and complement $C_3(B_1C)$ were found to be positive by the immunofluorescent technique. In five of the eight specimens, IgM and IgA were stained to be positive while in three of them IgG was positive. Based on these results, the possible role of HB virus in the pathogenesis of this disease was discussed.

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