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Liver disease—a prominent cause of serum IgE elevation

E. VAN EPPS, G. HUSBY, R. C. WILLIAMS, JR & R. G. STRICKLAND *Divisions of Gastroenterology and Immunology, Department of Medicine and Microbiology, University of New Mexico, School of Medicine, Albuquerque, New Mexico* 87131, *U.S.A.*

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SUMMARY

Serum IgE concentrations were elevated in thirty-seven out of sixty-seven patients (55%) with acute or chronic liver disease of widely differing aetiology. The mean IgE concentrations in these patients showed an eight-fold increase above that observed in control subjects. Increased IgE levels in patients with liver disease occurred in the absence of eosinophilia, clinical evidence of atopy or other known causes of IgE elevation. No IgE-containing plasma cells were detected in the liver biopsies from thirty-two of the sixty-seven patients tested. Peripheral blood T cells were significantly decreased from normal in the patients with liver disease, but no correlation emerged between serum IgE levels and absolute peripheral blood T-cell numbers. These findings emphasize the importance of liver disease as a significant cause of serum IgE elevation.

INTRODUCTION

Hypergammaglobulinaemia is a prominent accompaniment of both acute and chronic liver disease. Variable increases in serum IgG, IgA and IgM immunoglobulins have been reported in acute viral hepatitis (Dudley *et al.*, 1973; Ajdukiewica *et al.*, 1972), in chronic hepatitis of viral or idiopathic cause (Husby *et al.*, 1973; Feizi, 1968), and in hepatic cirrhosis including that attributed to alcohol (Wilson, Onstad & Williams, 1969). Increased serum IgE levels have been previously described in atopic states (Johansson, 1967), parasitic infestation (Johansson, Mellbin & Vahlquist, 1968; Hoggarth-Scott, Johansson & Bennich, 1969; Dessaint *et al.*, 1975), Wiscott–Aldrich syndrome (Bergland *et al.*, 1968), and more recently in patients with interstitial nephritis (Ooi *et al.*, 1974). Earlier studies of serum IgE levels in patients with liver disease utilized less sensitive techniques than those currently available for measurement of this immunoglobulin (Heiner & Rose, 1970; Brown, Lansford & Hornbrook, 1973) and the results were conflicting. In the present study, we report striking elevations of serum IgE in a large group of patients with well-characterized acute or chronic liver disease of diverse aetiology using a sensitive radioimmunoassay technique.

MATERIALS AND METHODS

Patients. The study population consisted of sixty-seven patients who had undergone percutaneous liver biopsy to evaluate the presence of clinical and/or laboratory evidence of hepatic dysfunction. This population consisted of forty-one males with an average age of 43, range 22–81, and twenty-six females with an average age of 46, range 21–80. Forty-six patients had alcoholic liver disease including three with fatty liver, twenty-nine with alcoholic hepatitis and fourteen with alcoholic cirrhosis. Twenty-one patients had non-alcoholic liver disease. This group included eleven with acute hepatitis (viral in five, reactive in four, drug-induced in one and granulomatous in one), five with chronic hepatitis (chronic persistent in three, chronic

Correspondence: Dr D. Van Epps, Department of Medicine, University of New Mexico, School of Medicine, Albuquerque, New Mexico 87131, U.S.A.

active in two), and five with cirrhosis (cryptogenic in four and associated with hepatitis B antigen in one). Review of these patients' histories for evidence of atopic disorders (drug allergy, hay fever or asthma) revealed that six of the sixty-seven patients had an allergic history. None of the patients had peripheral blood eosinophilia at the time of study.

Methods. Serum IgE concentrations were determined using a Pharmacia Phadebas IgE testing kit (Pharmacia Laboratories, Piscataway, New Jersey). This test utilizes an insolubilized anti-IgE antibody and the competitive inhibition of its binding to an ^{125}I-labelled IgE immunoglobulin. Standards for this assay were calibrated against immunoglobulin E1 68/341 from the WHO International Reference Center. The arithmetic mean IgE concentration in a group of forty-one healthy control subjects without clinical evidence of liver disease was 103 ± 85 u/ml and the geometric mean, 86 u/ml (range 0·5–900 u/ml). The control population consisted of thirty-one males with an average age of 42 years, range 22–55, and ten females with an average age of 40 years, range 25–83. Eight normal subjects had an allergic history as previously defined. All sera were tested for anti-IgE antibody using the technique of Williams *et al.* (1972). This technique measures agglutination of erythrocytes coated with three separate IgE myelomas. In addition, patient sera were also tested for circulating IgG antibodies directed against IgE immunoglobulin as measured by histamine release (May *et al.*, 1970), since such antibodies have recently been shown to interfere with accurate IgE determination using several radioimmunoassay techniques (Assem, 1975). Patient and control sera were tested at three concentrations (undiluted, 1:10 and 1:100) in conjunction with leucocytes obtained from allergic individuals. In each case, controls for serum alone and cells alone were subtracted from the total histamine release.

Serum IgG, IgA and IgM concentrations were determined by the Oudin tube technique (Wilson, Williams & Tobian, 1967). Serum IgD concentrations were measured by the Mancini technique using an IgD testing kit obtained from Meloy Laboratories (Springfield, Virginia).

Peripheral blood lymphocytes were obtained by Ficoll–Hypaque gradient centrifugation of heparinized venous blood as previously described (Böyum, 1968). Bone marrow-derived (B) lymphocytes were measured by direct immunofluorescence using monospecific antisera to IgG, IgA, and IgM (Pernis, Forni & Amanti, 1970). The sum of IgG, IgA, and IgM staining cells was taken to represent total B lymphocytes (Williams *et al.*, 1973). Thymus-derived (T) lymphocytes were determined by the sheep erythrocyte binding technique (Fröland, 1972; Jondal, Holm & Wigzell, 1972). Total number of B and T lymphocytes per mm^3 were calculated from differential white cell counts.

Percutaneous liver biopsies from thirty-two of the sixty-seven patients were examined by direct immunofluorescence (Husby *et al.*, 1973) for the presence of IgE-containing cells. The rabbit anti-human IgE antiserum used was made specific for the Fc portion of the IgE molecule by passage through an immunoabsorbent column prior to conjugation with FITC.

RESULTS

Serum IgE concentrations in the patients studied are shown in Figs 1 and 2. Thirty-seven of the sixty-seven patients tested demonstrated IgE levels above two standard deviations (s.d.) from the mean in normal controls. This included twenty-six of the forty-six patients (60%) with alcoholic liver disease and eleven of the twenty-one patients (57%) with non-alcoholic liver disease. No clear difference in the frequency of serum IgE elevation was apparent amongst the various types of liver disorder studied. There was also no association between measured serum IgE levels and history of atopic or allergic disorder among the patients studied. IgE concentrations above 1000 u/ml were observed in eleven of the sixty-seven patients and the highest level seen was in a patient with alcoholic hepatitis and cirrhosis (20,000 u/ml). Using the Wilcoxon rank sum test the mean IgE level in the sixty-seven patients (arithmetic mean 851 ± 2489 u/ml, geometric mean 300 u/ml) was significantly elevated ($P < 0{\cdot}001$) when compared to control values (arithmetic mean 103 ± 85 u/ml, geometric mean 86 u/ml). All sixty-seven sera were negative when tested for agglutinating antibody to erythrocytes sensitized with IgE. Five patients with serum IgE levels of greater than 800 u/ml were also tested for their ability to cause histamine release from IgE-sensitized peripheral blood basophils. Only one of these five patient sera caused histamine release significantly greater than baseline values obtained with normal sera. Thus, anti-IgE activity did not appear to be present in a majority of sera with quantitative elevations of IgE.

Liver biopsies from thirty-two of the sixty-seven patients including eight with serum IgE levels above 1000 u/ml were examined for IgE-containing cells, and studies were uniformly negative.

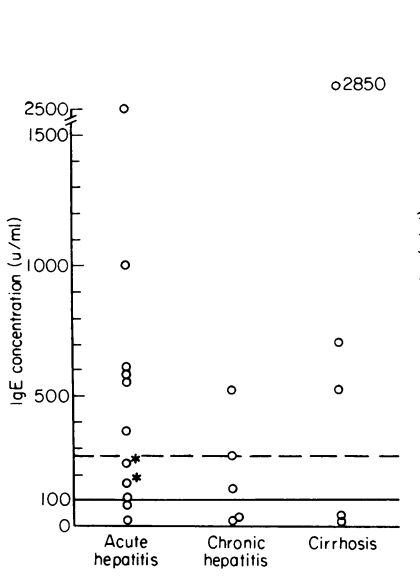

FIG. 1

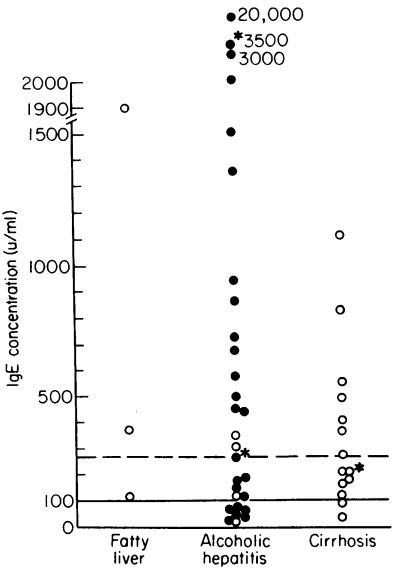

FIG. 2

FIG. 1. Serum IgE concentrations in patients with non-alcoholic liver disease. The solid horizontal line at 103 u/ml represents the mean of the forty-one normal controls and the dashed line, two standard deviations above this mean. Patients with allergic histories are marked with an asterisk.

FIG. 2. Serum IgE concentrations in patients with alcoholic liver disease. The closed circles indicate patients with both alcoholic hepatitis and cirrhosis and open circles indicate patients with only alcoholic hepatitis. Patients with allergic histories are marked with an asterisk. The solid horizontal line at 103 u/ml represents the mean of the forty-one normal controls and the dashed line, two standard deviations above this mean.

Mean serum IgG, IgA and IgM concentrations in the sixty-seven patients with liver disease were also significantly increased above normal values (Table 1). However, in several instances serum IgE levels were disproportionately increased when compared to the other immunoglobulins (Table 2).

The mean IgD concentration in the patients with liver disease did not differ significantly from the controls. In the patients, IgD levels ranged from 0 to 32 mg/100 ml with 68% between 0 and 8 mg/100 ml, while controls ranged from 0 to 34 mg/100 ml with 70% between 0 and 8 mg/100 ml.

The mean absolute numbers of peripheral blood B and T cells measured in patients and controls are shown in Table 3. T-cell numbers were significantly decreased ($P<0{\cdot}001$) in the patients with liver disease. However, total B-cell numbers and subpopulations of B cells did

TABLE 1. Mean serum immunoglobulin concentrations in controls and patients with liver disease

Subjects	IgE (u/ml)	IgG (mg%)	IgA (mg%)	IgM (mg%)	IgD (mg%)
Controls	103±85†	1278±361	282±128	110±49	8±11
	$P<0{\cdot}001$	$P<0{\cdot}001$	$P<0{\cdot}001$	$P<0{\cdot}001$	n.s.*
Liver disease	851±2489	1907±1093	404±194	276±202	8±8

* n.s. = Not significant.
† Mean ± one standard deviation.

TABLE 2. A comparison of serum immunoglobulins in patients with liver disease showing serum IgE concentrations of greater than 1000 u/ml

Subject	IgG (mg%)	IgA (mg%)	IgM (mg%)	IgE (u/ml)
A.G.	1750	1200	220	3000
F.W.	1525	580	190	20,000
L.K.	1300	740	235	3500
L.U.	1300	940	160	2000
T.M.	2200	580	310	1300
D.U.	2100	425	190	1100
J.P.	1300	740	250	1900
H.E.	1150	580	117	2500
A.H.	1150	520	215	1500
A.P.	1900	400	250	1000
P.M.	3400	200	120	2850
Normal controls	1278±361	282±128	135±65	103±85

TABLE 3. Peripheral blood B- and T-lymphocyte numbers in patients with liver disease and controls*

Subjects	Number tested	T cells/mm³	B cells/mm³	Cells with surface IgG/mm³	Cells with surface IgA/mm³	Cells with surface IgM/mm³
Controls	50	1706±607 $P<0{\cdot}001$	571±275 P = n.s.†	303±157 P = n.s.	104±81 P = n.s.	172±74 P = n.s.
Liver disease	53	1131±786	541±367	270±203	106±75	162±113

* Statistical analysis performed using t-test for difference between means.
† n.s. = Not significant.

not differ substantially or significantly from normal. A comparison of the absolute numbers of peripheral blood T cells with serum IgE concentrations in the patients studied showed no significant correlation between total T-cell numbers and IgE levels ($r = -0{\cdot}072$, $P>0{\cdot}9$). Similarly, no correlation between serum IgG, IgA or IgM concentrations and peripheral blood T-cell numbers was evident in the patients studied.

DISCUSSION

Previous studies have demonstrated that serum IgG, IgM and IgA concentrations are increased in liver disease (Dudley *et al.*, 1973; Ajdukiewicz *et al.*, 1972; Husby *et al.*, 1973; Feizi, 1968; Wilson *et al.*, 1969). It is evident from the present study that serum IgE levels are also greatly elevated in many patients with a variety of acute or chronic hepatic disorders.

The radioimmunoassay used in the present study involves the binding of IgE to Sepharose beads. The possibility that the serum of patients with liver disease might contain a blocking factor which would result in falsely elevated IgE levels was considered. Such inhibitors have been described in immunodeficient patients by Polmar, Waldmann & Terry (1973), and in patients with cancer by Jacobs *et al.* (1972). No agglutinating anti-IgE activity was detected in the sera of patients with liver disease studied here; and only one of five patient sera tested with marked elevations of IgE resulted in release of histamine from IgE-sensitized leuco-

cytes. These findings make anti-IgE factors an unlikely explanation for elevation of IgE in the solid immunoadsorbent assay.

Elevated serum IgE concentrations were previously reported in nine out of eighteen patients with Laennec's cirrhosis (Heiner & Rose, 1970); in another study, IgE levels were normal in ten patients with chronic hepatitis or postnecrotic cirrhosis (Brown *et al.*, 1973). These studies, however, utilized techniques less sensitive than the assay used in the present report. More recently, Patterson *et al.* (1975) have described extreme polyclonal hyperimmunoglobulinaemia E and eosinophilia in a patient with alcoholism and fatty liver. Our patients with elevated serum IgE concentrations did not show eosinophilia. Moreover, the occurrence of elevated serum IgE levels did not clearly relate to the presence of known allergies in the patients studied.

A previous report by Heiner & Rose (1970) recorded elevated IgD concentrations in patients with Laennec's cirrhosis; however, in the present study, mean IgD concentrations did not differ significantly between patients with liver disease and controls. Furthermore, the range of IgD levels observed in our patients was similar to that found in healthy subjects by Rowe & Fahey (1965). We cannot explain the differing results obtained in our study compared to that of Heiner & Rose (1970); nor is it apparent why IgD concentrations remain normal in comparison to all other immunoglobulin classes in patients with liver disease.

The mechanism of increased serum immunoglobulins in liver disease has been extensively investigated but remains obscure. Theoretically, elevated immunoglobulins may arise from increased immunoglobulin synthesis or decreased immunoglobulin catabolism. The latter could explain the extreme elevation of IgE since this immunoglobulin has the highest turnover rate per day (Waldmann *et al.*, 1972). Evidence to date does not support this possibility since it has been shown that the catabolic rate of gamma globulin is not decreased in liver disease (Havens *et al.*, 1953; Havens *et al.*, 1954). Further studies of specific immunoglobulin turnover rates are, however, needed to fully resolve this question.

Triger & Wright (1973) have suggested that the damaged liver may lose its filtering capacity and allow many antigens access to the immune system which would result in increased immunoglobulin synthesis. Earlier studies by Kent *et al.* (1957) and Glagou, Kent & Popper (1959) provide evidence for increased immunoglobulin synthesis in the lymph nodes and spleen in both experimental and naturally acquired liver disease. The normal peripheral blood B-cell numbers in liver disease recorded here and in earlier studies (DeHoratius, Strickland & Williams, 1974; Bernstein *et al.*, 1974) indicate that the enhanced immunoglobulin synthesis is not reflected in an increase in the circulating B-cell population. Hepatic immunoglobulin containing cells present in many forms of liver disease (Husby *et al.*, 1973; Hadziyannis *et al.*, 1969) may also contribute to serum immunoglobulin levels. This potential source for elevated IgE was not detected in the present study.

A decrease in circulating T cells appears to be a feature of many different forms of liver disease (DeHoratius *et al.*, 1974; Bernstein *et al.*, 1974). Furthermore, animal studies have clearly documented the existence of a T-cell subpopulation (suppressor T cells) which modify B-cell responses to antigenic stimulation (Katz *et al.*, 1974; Gershon, Maurer & Merryman, 1973). Increased serum immunoglobulin in patients with liver disease might, therefore, result from a depletion of the suppressor T-cell population. In the present study, no significant correlation between immunoglobulin levels and peripheral blood T-cell numbers was observed. However, these studies have involved measurement of total T-cell numbers which may not accurately reflect more subtle changes in T-cell subpopulations. Application of a recently described method for measuring suppressor T-cell function in man (Waldmann *et al.*, 1974) might define more clearly the presence of a defect in lymphocyte control mechanisms in patients with liver disease.

The hyperglobulinaemia of liver disease, therefore, appears to include elevations in all immunoglobulin classes with the exception of IgD. The present study suggests that the degree

of increase in some patients may be greatest in the IgE immunoglobulin class. Separate control mechanisms for IgG and IgE antibody involving suppressor or helper T lymphocytes have been recently reported in mice (Tada & Takemori, 1974) and might be invoked to explain the disproportionately large elevation of IgE observed in some of the patients studied. From a practical standpoint, our present observations indicate the importance of considering the presence of liver disease in any studies involving the measurement of serum IgE levels.

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