

Increased serum IgE in alcohol abusers

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Summary

Background It has been reported that total serum IgE is increased in patients with alcoholic cirrhosis, but it is not clear if this fact is related to alcoholic liver disease or to alcohol intake.

Objective To measure serum IgE in a group of chronic alcoholics with different stages of liver injury in order to elucidate if IgE increase is related to alcoholic liver damage.

Patients and methods Total serum IgE was determined by enzyme immunoassay in 186 chronic alcoholic patients (137 male/49 female) and 101 healthy controls. Patients and controls with known reasons for IgE elevation were excluded. Among alcoholic patients, 24 had fatty liver, 28 hepatic fibrosis, 29 alcoholic hepatitis, and 67 liver cirrhosis (38 patients were not evaluable concerning liver injury).

Results Total serum IgE was found to be increased in alcoholics (median 154.5 IU/mL, range 1–7329 IU/mL) with respect to healthy controls (median 20 IU/mL, range <1–1417 IU/mL) ($P < 0.001$). IgE increase was moderate (180–1000 IU/mL) in 60 alcoholics (32.3%) and marked (> 1000 IU/mL) in 27 (14.5%). Male alcoholics had higher IgE levels than females (median 191 IU/mL and range 1–7329 IU/mL vs 105 IU/mL and range 2–2189 IU/mL) ($P = 0.009$). On logistic regression analysis, alcoholism, male sex and younger age (but not smoking) were independently associated with higher IgE levels. No clear relationship was noted between serum IgE and severity of alcoholic liver disease. Thus, no correlation was observed between IgE and parameters of liver function (serum bilirubin, albumin or prothrombin index). Likewise, IgE concentrations were not significantly different in patients with liver cirrhosis with respect to patients with less severe liver disease. Serum IgE was increased (> 180 IU/mL) in 47.8% of cirrhotics and in 44% of patients without liver cirrhosis. In contrast, other immunoglobulins (IgG, IgA and IgM) were significantly correlated with liver dysfunction.

Conclusion Chronic alcoholism should be considered as a cause of increased total serum IgE, regardless of the severity of the underlying liver disease.

Keywords: serum IgE, alcohol abusers, alcoholic liver damage, increased IgE levels

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Introduction

Increased serum immunoglobulins are a frequent accompaniment of both acute and chronic liver diseases. In some instances, the increase is rather selective, affecting preferentially a particular immunoglobulin class. Elevated

serum IgM in acute hepatitis A [1,2] or primary biliary cirrhosis [3], and increased serum IgA in alcoholic liver disease [4,5] are examples of this.

Most available data on hypergammaglobulinemia in liver disease concern IgG, IgA and IgM but there is a scarcity of data regarding IgE. Early studies reported striking elevations of serum IgE in many patients with a variety of acute and chronic hepatic disorders [6], suggesting that increased serum IgE represented only a

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part of the polyclonal hypergammaglobulinemia of such disorders. However, further studies have shown that IgE is not uniformly elevated in liver diseases. As far as acute liver injury is concerned, there are reports of increased serum IgE levels in both acute hepatitis A and B, which may decrease during recovery [1,2]. Similarly, serum IgE values have been found to be elevated in untreated chronic active hepatitis of undefined aetiology [7]. However, the situation is different in chronic advanced hepatic disease (liver cirrhosis). Serum IgE has been reported to be normal in patients with non-alcoholic cirrhosis [2,8,9] and even low (<10 IU/mL) in about two-thirds of patients with primary biliary cirrhosis [10]. In contrast, there is increasing evidence that serum IgE is elevated in many patients with alcoholic cirrhosis. Heiner and Rose were the first to observe that IgE was raised in nine out of 18 patients with chronic advanced alcoholic liver disease [11]. Since then, several studies have reported similar results [1,6,7,10,12,13]. Nevertheless, most of these studies did not focus on alcoholic liver disease and included few cases of alcoholic patients grouped with other kinds of liver injury [1,7,10,12,13]. In 1980, Smith *et al.* measured serum IgE in 42 chronic alcoholics and found it elevated in cases of liver fibrosis or cirrhosis with respect to patients with alcoholic hepatitis and controls [14]. In 1983, Hällgren and Lundin observed that mean serum IgE was increased in 106 chronic alcoholics compared with controls [15]. In their study, no clear relationship was seen between IgE levels and parameters of liver dysfunction but no liver biopsy was performed and, hence, the possibility that subclinical liver involvement influenced IgE levels was not excluded [15]. Recently, we have studied 52 patients with complicated liver cirrhosis and have also observed that IgE was increased in about half of chronic alcoholics, compared with less than 10% of non-alcoholic cirrhotics or normal subjects [9]. Therefore, serum IgE could have some usefulness to determine the aetiology of the cirrhosis in a given patient. In this sense, its specificity and positive predictive value were higher than those of IgA, albeit its sensitivity was lower [9]. In the same study, no relation was observed between IgA and IgE increment in alcoholic cirrhotics, thus suggesting that their mechanisms are different [9].

In summary, there is an overall association between chronic alcoholism and an increase in IgE but it is not clear whether this fact is related either to chronic alcoholic liver disease or to alcohol intake itself [16]. In the first case, serum IgE elevation would be a mere part of hypergammaglobulinaemia of alcoholic liver cirrhosis. In the second, IgE increase could be related to immunological effects of ethanol. Thus, the present study was aimed to evaluate total serum IgE in a large series of

chronic alcoholics with different stages of liver injury in order to elucidate if elevation in serum IgE is specifically related to alcoholic liver damage or to alcohol ingestion.

Patients, materials and methods

Patients

One hundred eighty-six consecutive patients, 137 men and 49 women (median age 44 years, range 17–82 years), admitted to the Department of Internal Medicine during a 18-month period due to complications of chronic ethanol intake were enrolled in the study. Clinical details of the alcoholic patients (divided into males and females) are summarized in Table 1. All the patients (except two cases, aged 17 and 19 years — the only two teenagers in the disease group —, who had only a 3-year history of alcohol abuse) acknowledged an alcohol intake greater than 80 g per day over a minimum of 5 years. Thus, all cases met criteria for alcoholism [17]. Reasons for hospital admission were as follows: alcohol abstinence syndrome in 99 cases, complications of liver cirrhosis (ascites, encephalopathy or variceal bleeding) in 51 cases, acute pancreatitis in 11 cases and miscellaneous causes (mostly detection of liver biochemical changes and aspiration pneumonia) in the remaining 25 cases. Most patients (145 cases, 77.9%) came from a rural environment.

Liver biopsy was performed in 96 patients, of whom 24 had steatosis, 28 fibrosis, 29 alcoholic hepatitis and 15 liver cirrhosis. Liver biopsy could not be performed in 52 patients due to coagulopathy but ascites, oesophageal varices, uneven surface of the liver on echography, and persistently low prothrombin indexes were present in all of them and the patients were also considered cirrhotic. Liver biopsy was not done in the remaining 38 patients either because liver dysfunction was minimal or because they refused. They were considered to have 'miscellaneous liver disease'. Thus, only 148 cases were considered to have evaluable liver injury (Table 2). Cirrhotic patients were classified according to the Child-Pugh score (which includes albumin, Quick's time, bilirubin, presence of ascites and encephalopathy) as class A, B or C, the latter representing poorer hepatic function and, thus, worse prognosis [18].

Thirteen patients (6.9%) had serum antibodies against hepatitis C virus. Nineteen patients had serological evidence of past hepatitis B virus infection (HBc-Ab with or without HBs-Ab). Two more patients had detectable serum HBsAg but without evidence of active viral replication (all viral markers were determined by ELISA, Abbott Labs, Chicago, IL, USA).

A total of 101 healthy non-alcoholic volunteers, 56

Table 1. Summary of clinical data in male and female alcoholics

	Male alcoholics (<i>n</i> = 137)	Female alcoholics (<i>n</i> = 49)
<i>Epidemiological data</i>		
Age (years)	43 (17–82)	46 (19–75)
Abstinence syndrome	54.7%	49.0%
Smoking habit	69.3%	8.2%***
HCV antibody	9.4%	2.1%
<i>Biochemical/immunological parameters</i>		
Bilirubin (mg/dL)	1.2 (0.3–16)	1.7 (0.4–26)*
Albumin (g/dL)	3.6 (1.5–5.2)	3.3 (1.8–4.8)
Prothrombin index (%)	92 (18–100)	72 (20–100)**
AST (U/L)	63 (10–803)	70 (14–998)
ALT (U/L)	38 (8–332)	35 (7–641)
GGT (U/L)	152 (13–4851)	156 (14–1669)
Multitest score [#]	8.0 (0–33)	1.0 (0–16)
Total gammaglobulin (g/dL)	1.4 (0.6–4.5)	1.8 (0.8–3.9)**
IgG (mg/dL)	1071 (405–3842)	1347 (782–2960)*
IgA (mg/dL)	391 (122–1910)	463 (109–1440)
IgM (mg/dL)	149 (31–1430)	277 (16–693)**
<i>Liver injury[@]</i>		
Liver cirrhosis	43.1%	50.0%
Fatty liver	13.7%	21.7%
Liver fibrosis	23.5%	8.7%
Alcoholic hepatitis	19.6%	19.6%

Data are expressed as percentage or as median and (range). HCV. Hepatitis C virus. ****P* < 0.001. ***P* < 0.01. **P* < 0.05 with respect to the other group. [#]performed in only 50 patients. [@]data available for only 148 patients.

Table 2. Age and serum parameters in different stages of alcoholic liver disease

	Age (years)	Albumin (g/dL)	Bilirubin (mg/dL)	Prothrombin (%)	IgA (mg/dL)	IgE (IU/mL)
Cirrhotics (<i>n</i> = 67)	50 (30–82)*	2.8 (1.5–4.2)**	3.1 (0.5–26)**	55 (18–95)**	750 (136–1910)**	175 (1–7329)
Non-cirrhotics (<i>n</i> = 81)	40 (19–75)	4.0 (1.9–5.2)	1.0 (0.3–11)	99 (54–100)	328 (109–915)	113 (3–5858)
– Fatty liver (<i>n</i> = 24)	39 (19–75)	4.0 (2.1–4.8)	1.0 (0.4–2.9)	100 (70–100)	325.5 (116–578)	265 (5–1947)
– Liver fibrosis (<i>n</i> = 28)	41 (23–66)	4.0 (2.1–4.8)	1.0 (0.3–11)	100 (54–100)	323 (170–915)	123 (21–5858)
– Alcoholic hepatitis (<i>n</i> = 29)	42 (24–64)	3.9 (2.9–5.0)	1.1 (0.5–2.8)	90 (70–100)	339 (109–867)	89 (3–3054)
Miscellaneous liver disease (<i>n</i> = 38) [#]	46.5 (17–82)	3.7 (2.3–4.8)	1.0 (0.3–12)	100 (50–100)	302 (147–742)	185 (2–3600)

Data are expressed as median and (range). ***P* < 0.001 with respect to every other subgroup. **P* < 0.001 with respect to every other subgroup, except for miscellaneous liver disease (*P* NS). Differences between subgroups of patients regarding IgE are not significant.

[#]Patients with unevaluable liver injury.

men and 45 women (median age 44 years, range 17–83 years) were used as controls. Liver tests were within normal limits in all cases.

Patients and healthy controls with conditions known to be associated with high serum IgE levels, such as personal history of atopic dermatitis, rhinitis, bronchial asthma, occupational diseases, allergic drug reaction in the previous six months, IgE myeloma, Hodgkin's disease, parasitic infestation, allergic contact dermatitis and bullous pemphigoid were excluded from the study. Information on smoking habit was recorded for both patients and controls. Ninety-nine alcoholics (51.1%) were smokers; 95 of them were men. Likewise, 28 controls (27.7%), 24 of them men smoked cigarettes regularly.

Liver tests

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyl transpeptidase (GGT), total bilirubin and albumin were assessed using a Hitachi 747 autoanalyser (Boehringer-Mannheim, Mannheim, Germany). Serum albumin was also used as an index of nutrition in patients without liver cirrhosis (and, thus, with low interference of liver dysfunction on albumin levels). Prothrombin index was calculated following Quick's method. Serum protein electrophoresis was done in agarose gel (Helena Instruments, Beaumont, TX, USA). Serum IgG, IgA and IgM were quantified by nephelometry (Array 360 System, Beckman Instruments Inc, Brea, CA, USA).

Delayed hypersensitivity skin tests

They were performed in only in 50 patients (40 men and 10 women) using a battery of seven antigens (Tetanus, Diphtheria, Group C *Streptococcus*, *Proteus mirabilis*, *Trichophyton mentagrophytes*, *Candida albicans* and *Tuberculin*, 0.03 mL each, all in a 70% w/v glycerin solution) injected intradermally using a standard device (Multitest IMC[®], Institut Mérieux, Lyon, France). Induration around each injection site was measured 48 h later and a final score was obtained by summing up mean diameters of all reactions larger than 2 mm.

Total serum IgE

Samples of serum were obtained from all alcoholic patients the day after admission. A second serum sample for IgE analysis was obtained in the hospital between 7 and 14 days later, (thus after a period of alcoholic abstinence) in 39 alcoholic subjects. Sera from patients and control subjects were stored at -20°C until

tested. IgE was determined by enzyme immunoassay in an Olympus PK-310 (Olympus Optical Co., Hamburg, Germany), using original reagents (Sanyo Chem. Industries, Kyoto, Japan). Lower and upper limits of IgE determination were 1 IU/mL and 1000 IU/mL, respectively. IgE values above the maximum were calculated using serial dilutions. For internal quality control, commercial lyophilized control sera (Liphocheck Immunoassay Controls, Biorad Diagnostics, ECS Division, CA, USA) were used. Coefficients of variation ranged between 3.2% and 3.5% for IgE values between 18 IU/mL and 395 IU/mL. For external quality control, blind lyophilized control sera from Wellcome Diagnostics (QAP Quality Control Program, Dartford, UK) were employed with satisfactory results. A total serum IgE level greater than 180 IU/mL was considered elevated according to the previous experience of our laboratory (it also approximated to the 85th percentile of control subjects in our study).

Statistical analysis

Chi-square test (with Yates' correction or Fisher's exact test when necessary) was used to compare dichotomous variables. Two-tailed Mann-Whitney *U*-test and Wilcoxon rank test (for paired data) were used to compare continuous variables because none of them fulfilled criteria of normality. For the same reason, data are expressed as median and range instead of mean $\pm$ SEM. In some cases, serum IgE levels were expressed as their logarithmic values. Univariate analysis was done using Spearman's rank correlation. In order to assess the effects of potential confounding variables, a multiple logistic regression model was developed using BMDPLR [19]. These variables were made to enter the model and estimated odds ratios and 95% confidence intervals were calculated from the coefficients. Quality of fit was verified by the Hosmer-Lemeshow method [20]. A *P*-value of less than 0.05 was considered statistically significant.

Results

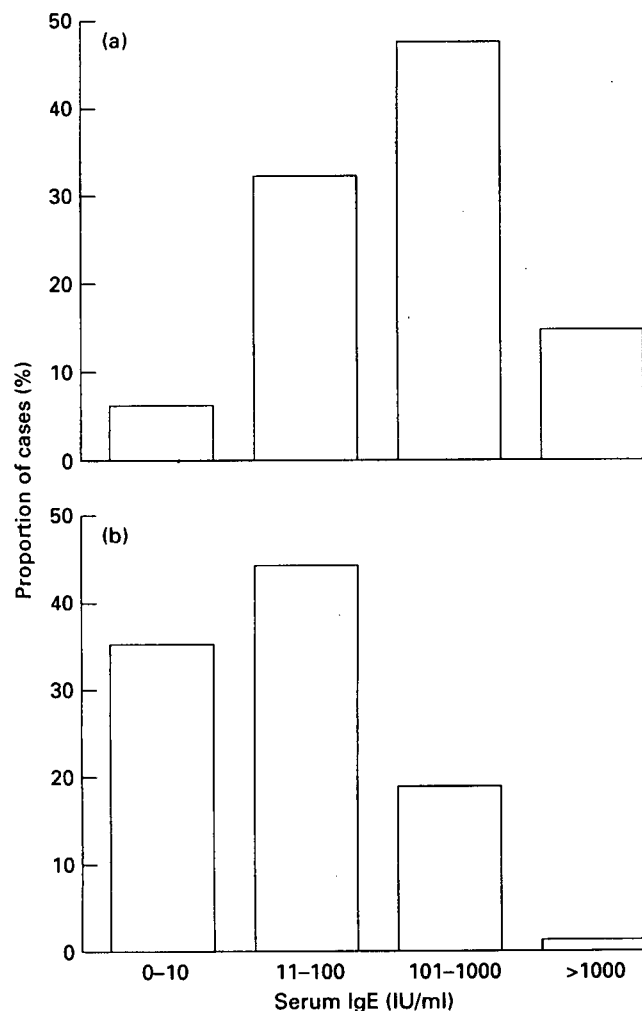
Total serum IgE was significantly increased in alcoholic patients with respect to healthy controls (Table 3). A histogram of IgE values for both groups is depicted in Figure 1. Considering 180 IU/mL as the upper limit of normal IgE range, 87 alcoholics (46.8%) presented higher levels, compared with only 13 controls (12.9%) ($P < 0.001$). Likewise, it is noteworthy that 27 alcoholics (14.5%) showed a very high IgE value (> 1000 IU/mL), compared with one of the controls (0.9%, $P < 0.001$).

Among alcoholic patients, significant differences in both liver function and IgE values were observed with

Table 3. Serum IgE values in alcoholic patients and healthy controls

	Alcoholic patients (<i>n</i> = 186)	Controls (<i>n</i> = 101)
Global	154.5 (1–7329)	20 (<1–1417)
Male	191 (1–7329)	37 (<1–1417)
Female	105 (2–2189)	12 (<1–627)

Data are expressed as median and (range). Alcoholics versus controls: $P < 0.001$. Male alcoholics versus male controls: $P < 0.001$. Male alcoholics versus female alcoholics: $P = 0.0094$. Female alcoholics versus female controls: $P < 0.001$. Male controls versus female controls: $P = 0.0090$.

**Fig. 1.** Histograms of IgE values in alcoholic patients (*n* = 186) and healthy controls (*n* = 101).

respect to sex. Females as a group had poorer liver function, as reflected by lower prothrombin indexes, along with higher serum bilirubin, total gamma-globulin, IgG and IgM (Table 1). Conversely, IgE values were significantly higher in male alcoholics (Table 3). As a matter of fact, 71 men (51.8%) had IgE levels > 180 IU/mL, compared with only 16 (32.7%) women ($P = 0.020$). Nevertheless, both male and female alcoholics had increased IgE when compared with their respective controls (Table 3).

Alcoholic smokers had higher IgE levels (median 211 IU/mL, range 1–7329 IU/mL) than non-smokers (median 109 IU/mL, range 2–3201 IU/mL) ($P = 0.0063$). This created a somewhat confounding situation, since the majority of males were smokers but, in contrast, only a minority of females smoked regularly. Besides, it is well-known that both male sex and smoking habit are associated with higher total serum IgE levels [21–24]. Thus, a multivariate analysis was performed to elucidate the interactions among the variables age, sex, alcoholism, and smoking habit, and their utility in predicting a high (> 180 IU/mL) IgE level. The results are represented in Table 4. Briefly, it was observed that alcoholism, male sex, and younger age were associated with high IgE values but there was no interaction amongst them, while the influence of smoking was not significant. The strongest influence seemed to be that of alcoholism. In fact, even when only non-smokers were considered, male alcoholics had higher IgE levels than male controls (median 117 IU/mL and range 10–3201 vs median 46 IU/mL and range < 1 –1417 IU/mL respectively, $P = 0.0014$), and the same was observed for females (median 105 IU/mL and range 2–2189 vs median 9 IU/mL and range < 1 –627 IU/mL, respectively, $P < 0.001$).

There was no clear relationship between serum IgE and either the severity of underlying alcoholic liver disease or hepatic necro-inflammatory activity. As is shown in Table 5, serum IgE did not correlate either

Table 4. Logistic regression analysis. Factors that can predict a high IgE value (> 180 IU/mL)

Variable	Standard coefficient	Odds ratio	95% Confidence interval	<i>P</i> -value
Alcoholism	1.649	5.20	2.68–10.1	0.0000
Male sex	0.740	2.10	1.05–4.18	0.0361
Age	–0.019	0.98	0.96–1.00	0.0481
Smoking	0.041	1.04	0.56–1.91	0.8927
Constant	–1.454			

Table 5. Spearman's rank correlations between serum immunoglobulins and other immunological and liver function parameters in alcoholic patients

	IgG	IgA	IgM	IgE
Bilirubin	0.515**	0.523**	0.376**	0.111
Prothrombin index	-0.666**	-0.635**	-0.383**	-0.077
Albumin	-0.441**	-0.523**	-0.140	-0.166
AST	0.186*	0.186*	0.268*	-0.019
ALT	-0.025	-0.097	0.128	-0.089
GGT	-0.118	-0.003	0.152	-0.023
Multitest score [#]	-0.108	-0.110	-0.099	-0.117
Gammaglobulin	0.907**	0.728**	0.561**	0.013
IgG	1.000	0.631**	0.478**	0.044
IgA		1.000	0.337**	0.123
IgM			1.000	-0.054

** $P < 0.001$; * $P < 0.02$; [#]performed in only 50 patients.

with parameters of liver function (bilirubin, albumin and prothrombin index) or with liver enzymes (AST, ALT and GGT). This was not the case for the other immunoglobulins (IgG, IgA and IgM), the levels of which correlated fairly well with parameters of liver injury. Similarly, IgG, IgA and IgM but not IgE were significantly correlated amongst themselves and with total gammaglobulin. Moreover, IgE values were not significantly different in patients with liver cirrhosis with respect to patients with less severe liver disease (Table 2). Only when patients with more advanced cirrhosis (Child-Pugh class C) were considered apart ($n = 34$) was IgE increased as compared with the rest of cirrhotics ($n = 33$) (median 289 IU/mL and range 27–7245 IU/mL, vs median 89 IU/mL and range 1–7329 IU/mL) ($P = 0.012$). In contrast, serum IgA concentrations were clearly higher in patients in liver cirrhosis (Table 2). Serum IgA was found increased (> 312 mg/dL) in 91.0% of cirrhotics, and IgE (> 180 IU/mL) in only 47.8% of them.

No difference in IgE level was observed between patients with and without hepatitis C virus infection. Likewise, no correlation was observed between IgE and delayed hypersensitivity tests (Multitest-IMC[®] score) (Table 5). Skin test scores were similar in patients with high IgE levels (> 180 IU/mL) (median 6 and range 0–18, $n = 24$) and in patients with normal IgE values (median 8 and range 0–33, $n = 26$) ($P = \text{NS}$). When serum albumin was evaluated as an index of nutrition in patients without liver cirrhosis, no difference was observed between cases with high (> 180 IU/mL) and normal IgE levels (median 4.0 g/dL and range 1.9–5.2 g/dL, vs median 3.9 g/dL and range 2.1–4.8 g/dL, respec-

tively, $P = \text{NS}$). Likewise, no significant correlation was observed between albumin and IgE in any group of patients. Patients of rural origin had a trend to higher IgE than urban cases (median 159 IU/mL and range 3–7329 IU/mL vs median 91 IU/mL and range 1–2247 IU/mL), albeit the difference was not significant. The cause for hospital admission was not associated with significant differences in IgE levels. The main cause was alcohol abstinence syndrome. It may be remarkable that patients admitted because of alcohol withdrawal syndrome had IgE values (median 129 IU/mL, range 3–5858 IU/mL) similar to the remaining patients. IgE was found to be increased in 43 out of 99 patients with abstinence syndrome (43.4%), a proportion similar to that of the rest of patients (44 out of 87, 50.4%) ($P = \text{NS}$).

Serum IgE tended to decrease during hospital admission and subsequent alcohol abstinence. Two serial IgE determinations could be obtained in 39 patients. In those cases, median IgE in the first serum sample was 147 IU/mL (range 5–3054 IU/mL). In the second one (taken 7 to 14 days after the first one), median IgE was 106 IU/mL (range 12–2526 IU/mL) ($P < 0.001$). The second IgE value was lower than the first one in 29 out of 39 patients, with a mean decrease of 25.1% in such cases.

Discussion

The data presented suggest that total serum IgE is elevated in apparently non-atopic chronic alcoholics (patients with ethanol intake greater than 80 g per day over a minimum of 5 years and admitted to the hospital due to complications of alcoholism) respect to healthy controls. Roughly, IgE was increased in about a half of alcoholics, with levels which may be considered very high (> 1000 IU/mL) in about one of seven cases. Alcoholism increased the probability of a high serum IgE value (> 180 IU/mL) fivefold. Logistic regression analysis also suggested that IgE elevation was more related to alcohol itself than to cofactors such as smoking, which is a well-known cause of a moderate increase in IgE levels [21,23,24] frequently associated with alcoholism. Likewise, it seems improbable that hidden factors such as some parasitic infection may be the cause of the IgE increment in all patients. The only factor clearly associated with enhanced IgE levels in our series of alcoholics was male sex. This is not surprising since normal males usually have higher IgE levels than females [22]. Previous studies concerning IgE in alcoholics included few women or none at all [9,15], and so this sexual difference in drinkers had not been settled before.

Interestingly, increased serum IgE was not clearly related either to the severity of alcoholic liver damage or the necro-inflammatory activity within the liver. First,

no significant difference was observed in IgE levels amongst patients with liver steatosis, fibrosis, alcoholic hepatitis or cirrhosis. In contrast, IgE concentrations tended to be highest in fatty liver and lowest in alcoholic hepatitis. Only when cirrhotic patients were considered apart, serum IgE was found increased in cases with more advanced liver disease (Child-Pugh class C) respect to those with better liver function (Child-Pugh class A or B). Second, no correlation was demonstrated between serum IgE and the usual parameters of liver dysfunction (serum bilirubin, albumin, prothrombin, AST, ALT and GGT). Third, alcoholic women had more biochemical signs of hepatic damage than men in our study, but serum IgE levels were significantly higher in male alcoholics. The behaviour of serum IgE with respect to liver dysfunction was quite different from that of IgA, the other immunoglobulin selectively elevated in chronic alcoholics. As a matter of fact, serum IgA levels showed rather good correlation with serum bilirubin, albumin and prothrombin index. Furthermore, IgA was significantly higher in patients with liver cirrhosis with respect to those with fibrosis, steatosis or alcoholic hepatitis. All these data, along with the previously reported normality of IgE in non-alcoholic cirrhotics [9], suggest that increased IgE in alcoholics is neither the simple result of liver injury nor a mere part of the hypergammaglobulinaemia of chronic liver disease. For the same reasons, mechanisms of IgE and IgA changes in alcoholic liver disease are likely to be different.

The substantial decrease in serum IgE observed in most patients after a short period of abstinence, a fact reported before [14,15], may support that ethanol by itself could influence IgE levels. However, as far as acute alcohol ingestion is concerned, we have observed that a single intake of 80 g of ethanol in healthy non-alcoholic individuals does not modify serum IgE levels up to 36 h later (unpublished observations). The case is different in the present study, in which we dealt with patients with chronic alcohol intake. It could be argued that variable chronic ethanol intake could have justified the different IgE values in our patients. We did not evaluate the exact quantity of alcohol consumed per day in each case but patients admitted because of major alcohol withdrawal syndrome may be useful for this purpose. They were a rather large group with a very high regular daily ethanol intake (more than 150 g/day) [25] which was interrupted just 24–48 h before admission (and subsequent IgE determination). When evaluated alone, the findings in this subgroup of alcoholics were heterogeneous, with increased serum IgE in less than a half of cases. Thus, the influence of a large chronic ethanol ingestion on IgE levels is not uniform. At least, some kind of susceptibility to ethanol should exist since not all patients had an elevated IgE in our study.

The mechanism of increased total serum IgE associated with alcoholism remains unknown. Increased gammaglobulin in liver cirrhosis is supposed to be initiated by spillover of protein antigens from the gut that bypass reticuloendothelial cells in the liver and induce an antigenic stimulus to other organs, particularly the spleen [26,27]. This hypothesis might be attractive for explaining increased IgE in alcoholics because it is known that ethanol depresses Kupffer cell phagocytosis both in experimental animals [28] and man [29]. Nevertheless, in a previous study, we could not correlate serum IgE levels in cirrhotics either with hepatic reticuloendothelial activity or with sensitization to food antigens [9]. In addition, as mentioned before, the behaviour of IgE did not parallel that of immunoglobulins or total gammaglobulin in the patients in the present study. On the other hand, ethanol may have induced IgE synthesis through depression of T-lymphocyte function. Alcohol can be regarded as a true immunosuppressive drug [14] that can interfere with cell mediated immunity, which may in turn facilitate IgE production and development of allergic diseases [30]. Malnutrition, a common fact in alcoholics, might contribute to immunosuppression and subsequent IgE increase [31]. It is not easy to evaluate nutrition in alcoholics because most biochemical parameters may be affected by liver dysfunction, and our study did not focus on this subject. However, our results (using albumin as an index) do not support that malnutrition has played a major role in IgE elevation in these cases. Along the same line, we observed no relationship between IgE in alcoholics and cutaneous tests of delayed hypersensitivity. These are generally regarded as the single most useful tests for evaluating the T-cell system, but they seem too coarse to evaluate fine T-cell functions [32,33]. Besides, the effect of alcohol on IgE production could be rather selective. Induction of IgE synthesis probably requires two signals: one that is IgE isotype-specific and is delivered by interleukin-4, and another which is a B-cell-activating signal that can be delivered through a variety of pathways [34]. Thus, ethanol can induce profound changes in serum cytokine concentrations (particularly, interleukin-6 and interleukin-8) [35–39] which could in turn be involved in increased IgE production [40,41]. Finally, ethanol might be by itself the antigenic stimulus for IgE production. Ethanol or its metabolites (mostly acetaldehyde) may act as haptens, and modify hepatic proteins rendering them antigenic. It is known that circulating antibodies to acetaldehyde-protein adducts are present in patients with alcoholic liver disease [42]. Moreover, anaphylactoid reactions to ethanol do exist [43], and circulating anti-acetaldehyde-protein IgE antibodies have been described in patients with such reactions [44]. In our

opinion, all these aspects concerning the bases of raised IgE in alcoholics deserve further investigation.

In conclusion, our results support the proposal that chronic alcoholism (particularly in men and regardless of the severity of liver damage) be added to the list of non-allergic diseases associated with elevated total serum IgE when the latter is used as a diagnostic tool. The cause of such IgE increase and the reason why not all chronic alcoholics have high IgE values remain to be elucidated.

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