

Double (Honeybee and Wasp) Immunoglobulin E Reactivity in Patients Allergic to Hymenoptera Venom: The Role of Cross-reactive Carbohydrates and Alcohol Consumption

FJ Carballada,¹ A González-Quintela,² R Núñez-Orjales,¹ L Vizcaino,³ M Boquete¹

¹Department of Allergy, Hospital Xeral, Lugo, Spain

²Department of Medicine, Hospital Clínico Universitario, Santiago de Compostela, Spain

³Department of Biochemistry, Hospital Clínico Universitario, Santiago de Compostela, Spain

■ Abstract

Background: Immunoglobulin (Ig) E-mediated sensitization to N-glycans (cross-reactive carbohydrate determinants, CCDs) may induce double IgE reactivity to honeybee venom (HBV) and yellow jacket venom (YJV) in patients who are monosensitized to either of these venoms. Alcohol consumption is associated with increased IgE levels and possibly with sensitization to CCDs in the general population.

Objectives: This study investigated the factors associated with double (HBV and YJV) IgE reactivity in patients who are allergic to Hymenoptera venom, and in particular, alcohol consumption.

Methods: Ninety-one patients with Hymenoptera allergy (68 to HBV, 19 to YJV, and 4 to both venoms) were studied. Determinations included a multiallergen IgE test and IgE to HBV, YJV, natural (glycosylated) HBV phospholipase-A2 (nPLA2), recombinant (nonglycosylated) HBV phospholipase-A2 (rPLA2), MUXF (the N-glycan from bromelain), natural (glycosylated) rubber latex, total IgE. Double reactivity was defined as an IgE level >0.35 kU_A/L to HBV and YJV.

Results: Double reactivity was observed in 28/87 (32%) clinically monosensitized patients. Double reactivity was associated with high levels of total IgE, MUXF-specific IgE, nPLA2-specific IgE, latex-specific IgE, and false-positive results in the multiallergen IgE test, but not with rPLA2-specific IgE. Alcohol consumption was associated with double reactivity and with high levels of IgE to glycosylated allergens after adjusting for confounders in the multivariate analysis.

Conclusions: Sensitization to CCDs and clinically irrelevant double (honeybee and wasp) IgE reactivity are common among Hymenoptera venom-allergic patients who drink alcohol. A simple questionnaire about alcohol consumption could be useful when interpreting levels of specific IgE in these patients.

Key words: Hymenoptera venom allergy. Carbohydrate epitopes. Environmental factors. Immunoglobulin E. Cross-reactivity. Alcohol.

■ Resumen

Antecedentes: La sensibilización mediada por IgE a los N-glicanos (carbohidratos con reactividad cruzada, CCDs) puede inducir doble reactividad al veneno de abeja (HBV) y al veneno de avispa (YJV) en pacientes mono-sensibilizados a alguno de esos venenos. El consumo de alcohol se asocia con niveles elevados de IgE y posiblemente con sensibilización a CCDs en la población general.

Objetivo: En el presente estudio se han investigado los factores asociados a doble reactividad (a HBV y YJV) en pacientes alérgicos a veneno de himenópteros, especialmente el consumo de alcohol.

Metodos: Se estudiaron 91 pacientes con alergia a veneno de himenópteros (68 a HBV, 19 a YJV, y 4 a ambos venenos). Las determinaciones realizadas incluyeron IgE específica a HBV, YJV, fosfolipasa-A2 natural (glicosilada) de HBV (nPLA2), fosfolipasa-A2 recombinante (no glicosilada) de HBV (rPLA2), MUXF (el N-glicano de la bromelaina), latex natural (glicosilado), IgE total y un test de IgE multi-alérgico. Se definió la doble reactividad como la presencia de una IgE específica >0.35 kU/L frente a HBV y YJV.

Resultados: Se observó doble reactividad en 28/87 (32%) de los pacientes clínicamente mono-sensibilizados. La doble reactividad se asoció con niveles altos de IgE, de IgE específica a MUXF, a nPLA2, a latex y con falsos positivos del test multialérgico, pero no con IgE frente a rPLA2. El consumo de alcohol se asoció con doble reactividad y con niveles altos de IgE frente a alérgenos glicosilados tras ajustar por factores de confusión en los análisis multi-variable.

Conclusiones: La sensibilización a CCDs y la doble reactividad (clínicamente irrelevante) frente a HBV y YJV son frecuentes en los pacientes alérgicos a himenópteros que beben alcohol. Un cuestionario simple sobre el consumo de alcohol podría ser útil a la hora de interpretar los niveles de IgE específica en los pacientes con alergia al veneno de himenópteros.

Palabras clave: Alergia a veneno de himenópteros. Carbohidratos. Factores ambientales. Inmunoglobulina E. Reactividad cruzada. Alcohol.

Introduction

N-glycans in many plant and invertebrate allergens are a common cause of immunoglobulin (Ig) E cross-reactivity in vitro and are commonly known as cross-reactive carbohydrate determinants (CCDs) [1-3]. Current evidence indicates that CCDs have poor activity in vivo; therefore, IgE sensitization to CCDs is considered clinically irrelevant, because sensitized individuals do not develop allergic symptoms when exposed to CCDs [1,4]. However, widespread cross-reactivity induced by CCDs interferes with the performance of in vitro allergy tests [1-3,5].

Hymenoptera stings are a probable cause of IgE-mediated sensitization to CCDs [6,7]. In turn, CCD sensitization causes in vitro double reactivity, namely, the presence of IgE to wasp (yellow jacket) venom (YJV) in patients who are only allergic to honeybee venom (HBV), and vice versa, because YJV and HBV glycoproteins share the same CCDs [8-10]. This double reactivity is important, because determination of specific IgE is a standard test for the diagnosis of Hymenoptera venom allergy in allergy clinics [11]. Recently, increased total serum IgE was shown to be associated with both sensitization to CCDs and clinically asymptomatic double reactivity to HBV and YJV [12].

Alcohol is a powerful immunomodulatory drug [13] and consumption is associated with increased serum levels of total IgE [14,15] and specific IgE to CCDs [16-19]. Heavy drinking, in particular, is associated with in vitro reactivity to pollens [16], plant food allergens [18], latex [17], and Hymenoptera venoms [16], and positive multiallergen test results [20] in populations of asymptomatic individuals (ie, individuals with no clinical manifestations of allergy). The aim of the present study was to investigate the factors associated with double (HBV and YJV) IgE reactivity in patients who are allergic to Hymenoptera venom, with special emphasis on alcohol consumption.

Methods

Study Population

The study included 91 consecutive patients (66 males [72%]; median age, 44 y [range, 16-75 y]) who were newly diagnosed with Hymenoptera venom allergy at a single

institution during a 3-year period (2005-2007). All participants had a systemic (Mueller grade I or higher) [21] reaction to honeybee sting, yellow jacket sting, or both. Patients were carefully classified as allergic to HBV (n=68), YJV (n=19), or both (n=4) after identification of the offending insect, tolerance to the other insect, and positive skin test results, following standard criteria [11]. No patients were receiving specific immunotherapy. Most patients (79%) lived in a rural environment. Thirty-four patients (29%) were current or former beekeepers. Fourteen (15%) were atopic, as shown by a history of typical respiratory symptoms and positive skin prick tests to inhalant allergens. All individuals consented to participate in the study, which was approved by the Institutional Review Board and conformed to the Declaration of Helsinki (Sixth Revision).

Main Determinations

Alcohol consumption was evaluated using standard drinking units [22], which is the sum of the number of glasses of wine, bottles of beer, and measures of spirits regularly consumed per week (each of these was considered 1 unit, or approximately equivalent to 10 g of alcohol). Similar to earlier reports [16,17], patients were classified as abstinent/occasional drinkers (0-1 units/wk), light-to-moderate drinkers (2-27 units/wk), or heavy drinkers (≥ 28 units/wk). Patients were classified as smokers when they regularly consumed at least 1 cigarette per day.

Total serum IgE was determined using chemiluminescent immunoassay (Immulate-2000, Siemens Medical Solutions, Llanberis, Gwynedd, UK). Specific IgE was determined using the Immuno-CAP-250 system (Phadia, Uppsala, Sweden) for the following allergens: HBV (i1), YJV (i3), natural (glycosylated) honeybee phospholipase-A2 (nPLA2), recombinant (nonglycosylated) honeybee phospholipase-A2 (rPLA2), MUXF (Ro214, the N-glycan from bromelain, a standard CCD marker) [1-3], and natural (glycosylated) rubber latex (NRL, *Hevea brasiliensis*, k82). The reportable range with this system is 0.01-100 kU_A/L. Following traditional classifications, IgE levels >0.35 kU_A/L were considered positive, and individuals with an IgE level >0.35 kU_A/L to both HBV and YJV were considered to have double in vitro reactivity. Determinations also included a multiallergen test (Phadiatop, Phadia), which measures IgE to a mixture of common inhalant allergens and was considered positive or negative according to the manufacturer's instructions.

Statistical Analysis

The χ^2 test (with trend analysis when appropriate) was used to compare proportions. The Mann-Whitney test was used to compare numerical variables between groups. The Spearman rank test was used to assess correlation. Logistic regression was used for multivariate analysis.

Results

Double IgE reactivity was observed in 28 of 87 (32%) clinically monosensitized patients. Clinically irrelevant

double reactivity was associated with higher levels of total IgE (Table 1). Among patients who were clinically monosensitized to HBV, levels of IgE to MUXF correlated with levels of IgE to YJV ($\rho=0.670$, $P<.001$). Among patients who were clinically monosensitized to YJV, levels of IgE to MUXF correlated with levels of IgE to HBV ($\rho=0.795$, $P<.001$). Double reactivity was strongly associated with higher levels of IgE to glycosylated HBV nPLA2, but was not associated with IgE to nonglycosylated HBV rPLA2 (Table 1).

Clinically irrelevant double reactivity was strongly associated with IgE reactivity to NRL. Levels of IgE to MUXF were strongly correlated at a 1:1 ratio with levels of IgE to NRL ($\rho=0.907$, $P<.001$) (Figure 1). Levels of IgE >0.35 kU_A/L to

Table 1. Demographic, Epidemiological, and Immunological Characteristics of Patients With and Without Clinically Irrelevant Double (Honeybee and Wasp) Immunoglobulin E Reactivity^{a,b,c}

	Patients With Double Reactivity ^a (n=28)	Patients With Single Reactivity to Either HBV or YJV (n=59)	P Value
Epidemiologic factors			
Age, y	41 (16-75)	48 (17-72)	.20
Sex, male	23 (82)	41 (69)	.21
Residence, rural	23 (82)	45 (76)	.53
Beekeeping	7 (25)	26 (44)	.08
Smoking	7 (27)	18 (30)	.73
Alcohol consumption, units/wk	23 (0-70)	7 (0-70)	.03
Clinical factors			
Mueller grade			
I	1 (4)	3 (5)	
II	8 (29)	22 (37)	
III	15 (53)	24 (41)	.72
IV	4 (14)	10 (17)	
Atopy ^d	6 (21)	8 (14)	.35
In vitro test results			
Positive multiallergen IgE test ^e	23 (85)	15 (26)	<.001
False-positive multiallergen IgE test ^f			
IgE to MUXF, kU _A /L ^e	0.75 (0-8.3)	0.01 (0-1.24)	<.001
IgE to natural rubber latex, kU _A /L ^e	1.1 (0.04-8.8)	0.04 (0.03-0.69)	<.001
IgE to natural HBV PLA2, kU _A /L	3.5 (1.1-40.3)	1.1 (0-41.3)	<.001
IgE to recombinant HBV PLA2, kU _A /L	0.81 (0-16.7)	0.59 (0-24.7)	.45
Total IgE, IU/mL ^e	144 (13-1265)	81 (4-609)	.002

Abbreviation: HBV, honeybee venom; Ig, immunoglobulin; MUXF, the N-glycan from bromelain; PLA2, phospholipase-A2; YJV, yellow jacket venom.

^aDouble reactivity is defined by an IgE level >0.35 kU_A/L to both venoms.

^bData are expressed as median (range) or absolute number (%).

^cPatients with clinically relevant double sensitization are not included.

^dClinical history of respiratory allergy plus positive skin prick tests to inhalant allergens.

^eData available for 27 and 57 individuals, respectively.

^fPositive multiallergen IgE test (Phadiatop) without evidence of atopy.

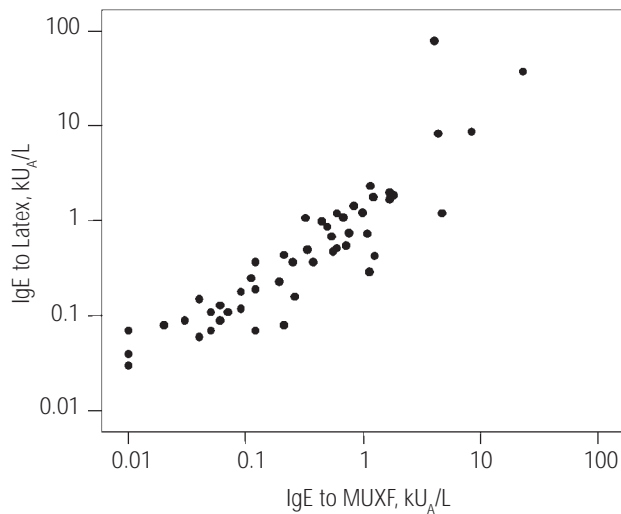


Figure 1. Correlation between serum levels of IgE to MUXF, the N-glycan from bromelain, and serum levels of IgE to natural rubber latex. Only cases with detectable levels of specific IgE are represented. All cases were included in the analysis. IgE indicates immunoglobulin.

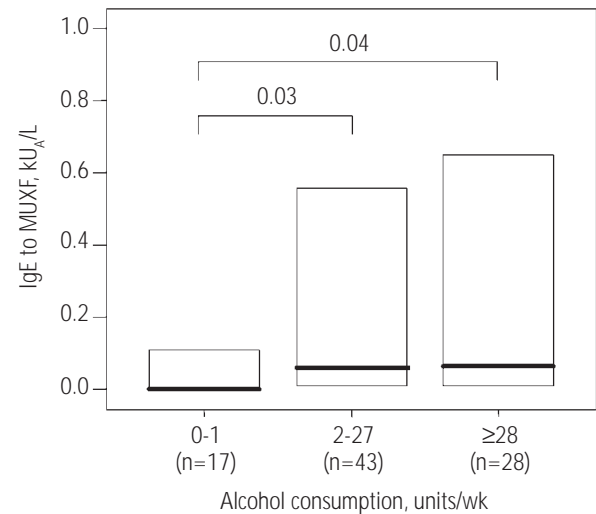


Figure 2. Serum levels of IgE to MUXF, the N-glycan from bromelain, in relation to alcohol consumption. Boxes represent the interquartile range and horizontal lines represent median values. All patients with an available determination were included. IgE indicates immunoglobulin.

Table 2. Factors Associated With Total and Specific Immunoglobulin E: Multivariate Analysis (Logistic Regression)^a

Factor	Double Reactivity (>0.35 kU _A /L) to Honeybee and Wasp Venom ^b	Positive (>0.35 kU _A /L) IgE to MUXF ^c	Positive (>0.35 kU _A /L) IgE to Natural Rubber Latex ^c	Positive Multiallergen IgE Test ^c	High (>100 IU/mL) Total IgE ^c
Age, y	0.966 (0.932-1.002)	0.939 (0.901-0.979) ^e	0.943 (0.908-0.980) ^e	0.930 (0.891-0.971) ^d	0.984 (0.951-1.017)
Sex (1=male)	0.94 (0.27-4.04)	0.95 (0.27-3.98)	0.87 (0.24-3.06)	0.67 (0.18-2.48)	2.82 (0.82-9.74)
Atopy (1=yes)	2.13 (0.55-8.22)	1.11 (0.24-4.98)	0.71 (0.16-3.17)	37.7 (3.50-407.3) ^e	5.57 (1.06-29.4) ^d
Residence (1=rural)	1.26 (0.34-4.62)	1.30 (0.33-5.16)	1.22 (0.33-4.46)	1.73 (0.45-6.63)	2.95 (0.80-10.8)
Beekeeping (1=yes)	0.39 (0.12-1.19)	0.48 (0.16-1.48)	0.61 (0.21-1.72)	0.95 (0.32-2.79)	0.68 (0.25-1.87)
Smoking (1=yes)	0.37 (0.10-1.32)	0.68 (0.20-2.24)	0.45 (0.14-1.46)	0.55 (0.16-1.80)	0.74 (0.24-2.27)
Alcohol, units/wk	1.053 (1.017-1.091) ^e	1.042 (1.006-1.079) ^d	1.038 (1.004-1.073) ^d	1.050 (1.013-1.087) ^e	0.972 (0.939-1.006)

^aData are expressed as odds ratios and 95% confidence intervals (within parentheses). Odds ratios were adjusted for all listed variables.

^bIncludes patients without clinically relevant double reactivity (n=87).

^cIncludes all patients with available determinations (n=88).

^dP<.05

^eP<.01

NRL were found in 30 of 88 (34%) patients for whom results were available. However, only 1 patient was truly allergic to latex. This patient, who had an NRL-IgE level of 80.0 kU_A/L and an MUXF-IgE level of 3.97 kU_A/L, was the only outlier in the correlation. Likewise, double reactivity was associated with positivity of the multiallergen IgE test (Phadiatop) (Table 1). In most cases, however, these positive results were not consistent with the clinical data (ie, in patients without evidence of sensitization to inhalant allergens) (Table 1). Double reactivity was associated with higher levels of total IgE (Table 1).

Clinically irrelevant double reactivity was associated with alcohol consumption (Table 1). The proportion of patients

with double reactivity increased from 17% (3/18) in alcohol abstainers/occasional drinkers to 29% (12/42) in light-to-moderate drinkers and to 48% (13/27) in heavy drinkers (P for trend, .02). The association between alcohol consumption and double reactivity was independent of potential confounders such as age, gender, smoking status, history of beekeeping, atopy, and residence (rural/urban) (Table 2). These factors were not associated with double reactivity (Tables 1 and 2).

Alcohol consumption was associated with increased levels of IgE to CCDs (MUXF) (Figure 2). The association between alcohol consumption and positivity of IgE to MUXF, positivity of IgE to natural rubber latex, and positivity of the

multiallergen IgE test was still present after adjusting for confounders (Table 2).

Discussion

This study shows that alcohol consumption, particularly heavy drinking, is associated with clinically irrelevant double (HBV and YJV) IgE reactivity in patients who are allergic to either HBV or YJV. Such double reactivity is a characteristic feature of CCD interference [8-10]. In fact, alcohol consumption was linked to increased levels of CCD-specific IgE. These findings were independent of potential confounders such as age, gender, smoking status, rural residence, and atopy.

The results are consistent with previous findings on CCD-IgE sensitization in epidemiological studies in general adult populations of asymptomatic individuals [16]. Importantly, this finding was confirmed in the clinical setting, where IgE to HBV and YJV is used as a diagnostic tool in patients with symptoms of Hymenoptera venom allergy. In this setting, clinical manifestations, identification of the offending insect, and skin tests are of paramount importance [11]. However, the results of IgE to HBV and YJV are routinely requested and should be interpreted with caution. Hymenoptera venom hypersensitivity is a high-risk allergy. Correct diagnosis of allergy to either HBV or YJV is necessary to indicate the appropriate immunization protocol. Double HBV and YJV reactivity should always raise the suspicion of interference by CCD [1,2,8-10]. Our results show that this interference should be taken into consideration, particularly in patients who drink alcohol.

Consistent with the results of previous reports [10,17,18], our findings showed that CCD sensitization and double venom reactivity were strongly associated with asymptomatic reactivity to CCD-bearing allergens such as NRL, but not to recombinant, nonglycosylated allergens. Similarly, CCD sensitization and double venom reactivity were strongly associated with discordant positivity of multiallergen IgE tests (ie, positive IgE tests to a mixture of inhalant allergens in patients with no history of respiratory allergy) [17,20]. Taken together, these results serve to emphasize both the common interference with *in vitro* tests and the clinical irrelevance of IgE to CCD *in vivo*.

The mechanisms underlying CCD sensitization and double IgE reactivity to HBV and YJV in alcohol drinkers are not entirely known. Alcohol consumption has been shown to induce a type 2 helper T cell deviation of the immune response [23-25], thus increasing serum IgE in observational studies [14,15,23] and in experimental animal models [24,25]. Children born to mothers who consumed alcohol during pregnancy show higher cord blood levels of IgE than those born to abstinent mothers [26]. Of note, individuals with high IgE levels are prone to IgE sensitization when exposed to a given allergen [27]. High total IgE levels are associated with sensitization to CCDs and subsequent *in vitro* reactivity to Hymenoptera venom [12]. In fact, double (HBV and YJV) reactivity was associated with total IgE levels in the present study. To the best of our knowledge, there is no evidence to support that

alcohol drinkers are more frequently exposed to Hymenoptera stings. Thus, it could be argued that alcohol drinkers are prone to become sensitized to CCD when exposed to Hymenoptera stings. Additional exposures favoring sensitization to CCD and subsequent double reactivity could include respiratory exposure to pollens [5] and, hypothetically, digestive exposure to CCD-bearing food allergens or allergens contained in beverages [28], including Hymenoptera-like allergens [29], which are favored by alcohol-induced gut permeability [30]. These hypotheses are currently under investigation.

Methodological issues to be considered include the quantification of alcohol consumption. Therefore, the system of standard drinking units is widely accepted and used [22]. Of note, similar interference by CCDs has been confirmed in alcohol drinkers from Portugal [17], which is near Spain, and in populations with different environmental exposures and drinking patterns such as Denmark [19]. The IgE assay method (ImmunoCAP system) is also a common reference, although some reports suggest that this system may be more prone to interference by CCDs than other commercial IgE assays [31].

In conclusion, clinically irrelevant double IgE reactivity is common in Hymenoptera-allergic patients who drink alcohol, probably due to interference by CCDs. Routine administration of a simple questionnaire to determine alcohol consumption could help physicians to interpret specific IgE levels in patients with Hymenoptera venom allergy.

Acknowledgments

The study was supported by the Instituto de Salud Carlos III (Fondo de Investigaciones Sanitarias, Spanish Ministry of Health, PI071173), and the Spanish Society for Allergy and Clinical Immunology (SEAIC)

References

1. Altmann F. The role of protein glycosylation in allergy. *Int Arch Allergy Immunol.* 2007;142:99-115.
2. Malandain H. IgE-reactive carbohydrate epitopes--classification, cross-reactivity, and clinical impact (2nd part) *Eur Ann Allergy Clin Immunol.* 2005;37:247-56.
3. van Ree R. Carbohydrate epitopes and their relevance for the diagnosis and treatment of allergic diseases. *Int Arch Allergy Immunol.* 2002;129:189-97.
4. Mari A, Ooievaar-de Heer P, Scala E, Giani M, Pirrotta L, Zuidmeer L, Bethell D, van Ree R. Evaluation by double-blind placebo-controlled oral challenge of the clinical relevance of IgE antibodies against plant glycans. *Allergy.* 2008;63:891-6.
5. Mari A. IgE to cross-reactive carbohydrate determinants: analysis of the distribution and appraisal of the *in vivo* and *in vitro* reactivity. *Int Arch Allergy Immunol.* 2002;129:286-95.
6. Aalberse RC, Koshte V, Clemens JG. Immunoglobulin E antibodies that crossreact with vegetable foods, pollen, and Hymenoptera venom. *J Allergy Clin Immunol.* 1981;68:356-64.

7. Kochuyt AM, Van Hoeyveld EM, Stevens EA. Prevalence and clinical relevance of specific immunoglobulin E to pollen caused by sting-induced specific immunoglobulin E to cross-reacting carbohydrate determinants in Hymenoptera venoms. *Clin Exp Allergy*. 2005;35:441-7.
8. Egner W, Ward C, Brown DL, Ewan PW. The frequency and clinical significance of specific IgE to both wasp (*Vespula*) and honey-bee (*Apis*) venoms in the same patient. *Clin Exp Allergy*. 1998;28:26-34.
9. Hemmer W, Focke M, Kolarich D, Wilson IB, Altmann F, Wohrl S, Gotz M, Jarisch R. Antibody binding to venom carbohydrates is a frequent cause for double positivity to honeybee and yellow jacket venom in patients with stinging-insect allergy. *J Allergy Clin Immunol*. 2001;108:1045-52.
10. Jappe U, Raulf-Heimsoth M, Hoffmann M, Burow G, Hubsch-Muller C, Enk A. In vitro hymenoptera venom allergy diagnosis: improved by screening for cross-reactive carbohydrate determinants and reciprocal inhibition. *Allergy*. 2006;61:1220-9.
11. Biló BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JN; the EAACI Interest Group on Insect Venom Hypersensitivity. Diagnosis of Hymenoptera venom allergy. *Allergy*. 2005;60:1339-49.
12. Sturm GJ, Schuster C, Kranzelbinder B, Wiednig M, Groselj-Strele A, Aberer W. Asymptomatic sensitization to hymenoptera venom is related to total immunoglobulin E levels. *Int Arch Allergy Immunol*. 2009;148:261-4.
13. Szabo G. Consequences of alcohol consumption on host defence. *Alcohol Alcohol*. 1999;34:830-41.
14. Hallgren R, Lundin L. Increased total serum IgE in alcoholics. *Acta Med Scand*. 1983;213:99-103.
15. González-Quintela A, Vidal C, Gude F. Alcohol, IgE, and allergy. *Addict Biol*. 2004;9:195-204.
16. González-Quintela A, Garrido M, Gude F, Campos J, Linneberg L, Lojo S, Vidal C. Sensitization to cross-reactive carbohydrate determinants in relation to alcohol consumption. *Clin Exp Allergy*. 2008;38:152-60.
17. Coutinho V, Vidal C, Garrido M, Gude F, Lojo S, Linneberg A, Gonzalez-Quintela A. Interference of cross-reactive carbohydrates in the determination of specific IgE in alcohol drinkers and strategies to minimize it: the example of latex. *Ann Allergy Asthma Immunol*. 2008;101:394-401.
18. Vidal C, Vizcaino L, Diaz-Peromingo JA, Garrido M, Gomez-Rial J, Linneberg A, Gonzalez-Quintela A. Immunoglobulin-E reactivity to a glycosylated food allergen (peanuts) due to interference with cross-reactive carbohydrate determinants in heavy drinkers. *Alcohol Clin Exp Res*. 2009;33:1322-8.
19. Linneberg A, Fenger RV, Husemoen LLN, Vidal C, Vizcaino L, Gonzalez-Quintela A. Immunoglobulin E sensitization to cross-reactive carbohydrate determinants: epidemiological study of clinical relevance and role of alcohol consumption. *Int Arch Allergy Immunol*. 2010;153:86-94.
20. González-Quintela A, Garrido M, Gude F, Campos J, Linneberg A, Lojo S, Vidal C. Discordant positive results of multiallergen immunoglobulin E tests in relation to cross-reactive carbohydrate determinants and alcohol consumption. *J Invest Allergy Clin Immunol*. 2009;19:70-1.
21. Mueller U. Insect sting allergy: clinical picture, diagnosis and treatment. New York: Gustav Fischer, Stuttgart; 1990; pp. 100-5.
22. Gual A, Martos AR, Lligona A, Llopis JJ. Does the concept of a standard drink apply to viticultural societies? *Alcohol Alcohol*. 1999;34:153-60.
23. González-Quintela A, Vidal C, Lojo S, Pérez LF, Otero-Antón E, Gude F, Barrio E. Serum cytokines and increased total serum IgE in alcoholics. *Ann Allergy Asthma Immunol*. 1999;83:61-7.
24. Heinz R, Waltenbaugh C. Ethanol consumption modifies dendritic cell antigen presentation in mice. *Alcohol Clin Exp Res*. 2007;31:1759-71.
25. Linneberg A, Roursgaard M, Hersoug LG, Larsen ST. Effects of alcohol consumption on the allergen-specific immune response in mice. *Alcohol Clin Exp Res*. 2008;32:553-6.
26. Bjerke T, Hedegaard M, Henriksen TB, Nielsen BW, Schiøtz PO. Several genetic and environmental factors influence cord blood IgE concentration. *Pediatr Allergy Immunol*. 1994;5:88-94.
27. Horner AA, Kawakami T. Allergen-independent immunomodulatory activities of immunoglobulin E. *Clin Exp Allergy*. 2009;39:304-6.
28. Kirschner S, Belloni B, Kugler C, Ring J, Brockow K. Allergenicity of wine containing processing aids: a double-blind, placebo-controlled food challenge. *J Investig Allergol Clin Immunol*. 2009;19:210-7.
29. Armentia A, Pineda F, Fernández S. Wine-induced anaphylaxis and sensitization to hymenoptera venom. *N Engl J Med*. 2007;357:719-20.
30. Parlesak A, Schäfer C, Schütz T, Bode CJ, Bode C. Increased intestinal permeability to macromolecules and endotoxemia in patients with chronic alcohol abuse in different stages of alcohol-induced liver disease. *J Hepatol*. 2000;32:742-7.
31. Guilloux L, Morisset M, Codreanu F, Parisot L, Moneret-Vautrin DA. Peanut allergy diagnosis in the context of grass pollen sensitization for 125 patients: roles of peanut and cross-reactive carbohydrate determinants specific IgE. *Int Arch Allergy Immunol*. 2009;149:91-7.

■ *Manuscript received January 4, 2010; accepted for publication February 10, 2010.*

■ **A González-Quintela**

Department of Internal Medicine
Hospital Clínico Universitario
15706 Santiago de Compostela, Spain
E-mail: arturo.gonzalez.quintela@usc.es