

Effect of prior hepatitis B infection on serum IgE levels in patients with human immunodeficiency virus infection

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Background: Advanced HIV infection is associated with increased serum IgE levels, which in turn have been associated with a poor prognosis. Our preliminary data revealed that serum IgE levels were significantly elevated in HIV seropositive injection drug users compared with HIV seropositive non-injection drug users. Since viral hepatitis is common among injection drug users and is itself associated with elevated serum IgE levels, we studied whether there was an association between increased serum IgE levels and positive hepatitis serology in HIV-seropositive patients.

Methods: A retrospective cross-sectional analysis was performed. The medical records of ambulatory HIV-infected patients in an ongoing study were reviewed. Forty-five patients had hepatitis A, B, and C serology performed. The associations between serum IgE levels and hepatitis A, B and C antibodies, CD4 and CD8 lymphocyte percentages, injection drug use, and sex were analyzed by univariate and multiple regression analyses.

Results: On univariate analyses, hepatitis B antibody was significantly associated with increased serum IgE levels in HIV-infected subjects ($P = .013$), especially in those with AIDS ($P = .015$). Multiple regression analyses controlling for CD4 lymphocyte percentages, sex, and drug use, confirmed that hepatitis B antibody status remained significantly associated with increased serum IgE levels ($P = .05$). There was no association of serum IgE levels with hepatitis A or C serology.

Conclusion: Prior hepatitis B infection is significantly associated with increased serum IgE levels in advanced HIV infection. The clinical implications of this finding deserve further study.

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INTRODUCTION

Advanced human immunodeficiency virus (HIV) infection is associated

with increased serum levels of immunoglobulin E (IgE), which in turn are associated with a poor prognosis.^{1–3} We and others have previously demonstrated that serum IgE levels were higher in HIV-seropositive injection drug users than in HIV-seropositive non-injection drug users.^{4,5} Constant antigenic stimulation from repeated injection of drugs or contaminants may cause increased serum IgE levels in injection drug users. Another possibility is that past or current infection with another pathogen may elevate serum IgE levels in HIV infection.

Hepatitis B virus infection is common in injection drug users and in persons with HIV,⁶ and has been associated with elevated serum IgE levels in non-HIV-infected subjects.^{7,8} We

therefore performed a retrospective study of 45 HIV-seropositive ambulatory patients to determine whether there was an association between increased serum IgE levels and past or current viral hepatitis infection.

METHODS

The medical records of 45 HIV-seropositive subjects who were part of an ongoing study of sinusitis and allergy in HIV infection were reviewed. All patients were from the Infectious Diseases Clinic at North Central Bronx Hospital, an inner city municipal hospital in New York City. Patients were carefully evaluated and excluded from the study if they had active allergic symptoms (ie, rhinitis, urticaria, and asthma), parasitic infection, collagen vascular disease or other syndromes associated with elevated serum IgE levels. Injection drug use status was determined by chart review and categorized as active/prior injection drug use or no prior/present injection drug use.

Acquired immune deficiency syndrome (AIDS) was defined according to the 1993 revised CDC criteria which include a CD4 lymphocyte percent $\leq 14\%$.⁹ Total serum IgE levels were measured by a solid-phase fluorescent assay (FAST: Bio Whittaker, Walkersville, MD).¹⁰ Peripheral blood lymphocytes were prepared from whole blood by Ficoll-Hypaque centrifugation followed by purification over a nylon-wool column, labeled with fluoresceinated monoclonal anti-CD4 antibodies and anti-CD8 antibodies and analyzed on a fluorescence-activated cell sorter, as previously described.¹¹ Hepatitis A IgG antibody, hepatitis B surface anti-

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body, and hepatitis C IgG antibody were determined by ELISA.¹²

Statistical analyses were performed using the Wilcoxon rank sum test for non-parametric data and two sample *t* test for parametric data. Data were analyzed as medians and arithmetic means. Multiple regression analyses were also performed using IgE and the log transformation of IgE. A *P* value of less than or equal to .05 was considered to be statistically significant.

RESULTS

All 45 subjects whose charts were reviewed had hepatitis serology performed. Of these, 28 (62%) were male, 31 (68%) were Hispanic, 13 (29%) were black, and 1 (2.2%) was white. Twenty seven (60%) were injection drug users.

Seventeen (37%) of 45 HIV-seropositive patients had positive hepatitis B surface antibody. Twenty-four (24) of 43 subjects (56%) had positive hepatitis A serology. Eighteen of 32 subjects (56%) had positive hepatitis C serology. Twenty-three patients had all three hepatitis serologies performed.

The HIV-seropositive subjects with hepatitis B surface antibody had significantly higher median serum IgE levels than the HIV-seropositive patients who were hepatitis B surface antibody negative. Only four of these patients were also hepatitis B surface antigen positive and all had serum IgE levels >100 IU/mL. None of the hepatitis B surface antibody-positive patients had symptoms or signs of active hepatitis. There was no correlation be-

tween hepatitis A or hepatitis C serology and serum IgE levels (Table 1). Of the 23 patients with all three hepatitis serologies performed simultaneously, the patients with positive hepatitis B surface antibody had the highest serum IgE levels compared with the patients with positive hepatitis A and C serologies but this difference did not reach statistical significance (Table 2).

The HIV-seropositive injection drug users who were also hepatitis B surface antibody positive had significantly higher serum IgE levels than the HIV-seropositive injection drug users who were hepatitis B surface antibody negative (Table 3). When stratified for injection drug use alone, we found no significant difference in serum IgE levels between injection drug users and non-injection drug users among our patients (71 versus 99 IU/mL, *P* = NS).

Thirty-seven of the 45 patients had CD4 lymphocyte percentages ≤14% with a diagnosis of AIDS. Median serum IgE levels were significantly increased in these patients who were hepatitis B surface antibody positive compared with the hepatitis B surface antibody-negative patients (Table 4). In the HIV-seropositive non-AIDS patients, the median serum IgE levels did not differ significantly between the patients with positive hepatitis B surface antibody and the patients with negative hepatitis B surface antibody.

CD8 lymphocyte percentages were available on 41 of 45 patients and ranged from 25% to 80% (median = 54%). Of these, the patients with in-

creased serum IgE levels (>100 IU/mL) had significantly decreased median CD8 lymphocyte percentages compared with the patients with normal serum IgE levels (Table 5). We did not find a significant relationship between hepatitis A, B, or C serology; serum IgE levels; and CD8 lymphocyte percentages.

The 28 males had significantly higher median serum IgE levels than the 17 females regardless of hepatitis B antibody status (245 versus 51 IU/mL, *P* = .026).

Multiple regression analyses using IgE and log transformed IgE revealed that hepatitis B antibody status was significantly associated with increased serum IgE levels (*P* = .05) in HIV-seropositive patients when controlling for CD4 lymphocyte percentages, sex, and drug use.

DISCUSSION

Serum IgE levels are increased in advanced HIV infection and have recently been proposed as a marker of HIV disease progression in children and adults.^{1,13} Although the cause of the elevated serum IgE levels remains unclear, several mechanisms have been suggested, including direct stimulation by HIV proteins¹⁴ and increased atopy in HIV infection.¹⁵

Increased levels of serum IgE occur in HIV-seronegative patients with untreated chronic active hepatitis, alcoholic liver disease and chronic liver disease associated with a positive hepatitis B surface antigen. The median serum IgE levels reported in patients with acute hepatitis and active chronic hepatitis were 480 μg/L and 360 μg/L, respectively. Although T lymphocytes were decreased in these patients, the association between CD4 lymphocytes and serum IgE levels were not described.^{7,8} In 1984, however, Vierucci et al¹⁶ reported significantly elevated serum IgE levels in beta-thalassemia patients with positive serologic markers for hepatitis B, and these patients had normal CD4 levels.

Epstein Barr virus infections have also been associated with increased serum IgE levels in non-HIV infected

Table 1. Serum IgE Levels and Hepatitis A, B, and C Antibody Status in 45 HIV Seropositive Subjects

Group*	N	Median IgE (range, IU/mL)	Mean, IU/mL	<i>P</i> Value†
Hepatitis A (+)	24	45 (0-4898)	352	NS
Hepatitis A (-)	19	99 (6-2772)	434	
Hepatitis B (+)	17	258 (14-4898)	659	.012†
Hepatitis B (-)	28	60 (0-2772)	329	
Hepatitis C (+)	18	45 (12-4898)	668	NS
Hepatitis C (-)	14	187 (0-500)	190	

* Hepatitis A serology available in 43 subjects, hepatitis B serology available in 45 subjects and hepatitis C serology available in 32 subjects.

† *P* value obtained by Wilcoxon ranked sum test.

Table 2. Serum IgE Levels in 23 HIV-Seropositive Patients with Simultaneous Hepatitis A, B, and C Serologies

Group	N	Median, (range, IU/mL)	Mean, IU/mL	*P Value
Hepatitis A (+)	10	39 (0–4898)	508	NS
Hepatitis A (–)	13	99 (0–4898)	323	
Hepatitis B (+)	8	140 (33–4898)	732	.09
Hepatitis B (–)	15	39 (0–2772)	260	
Hepatitis C (+)	12	38 (12–4808)	675	NS
Hepatitis C (–)	11	150 (0–209)	151	

* P value obtained by Wilcoxon rank sum test.

Table 3. Serum IgE Levels and Hepatitis B Antibody Status According to Drug Use in HIV-Seropositive Patients

Group	N	Median (range, IU/mL)	Mean, IU/mL	P Value
Injection drug users				
Hepatitis B (+)	12	242 (14–4898)	823	.027*
Hepatitis B (–)	15	39 (12–2772)	248	
Non-Injection drug users				
Hepatitis B (+)	5	289 (40–618)	297	NS
Hepatitis B (–)	13	96 (0–800)	173	

* P value obtained by Wilcoxon rank sum test.

Table 4. HIV Category and Serum IgE Levels According to Hepatitis B Surface Antibody Status

Group	N	Median (range, IU/mL)	Mean	P Value
HIV seropositive with AIDS				
Hepatitis B (+)	15	279 (14–4898)	733	.015*
Hepatitis B (–)	22	80 (6–2772)	285	
HIV seropositive without AIDS				
Hepatitis B (+)	2	137 (33–242)	137	NS
Hepatitis B (–)	6	55 (0–230)	62	

* P value obtained by Wilcoxon rank sum test.

Table 5. CD8% in HIV Seropositive Patients with Normal and Elevated Serum IgE Levels

Group	N	Median (range, %)	Mean	P Value
Normal IgE levels (IgE <100 IU/mL)	19	57% (28–80)	47%	.02*
Elevated IgE levels (IgE ≥100 IU/mL)	22	48% (25–70)	57%	

* P value obtained by Wilcoxon rank sum test.

patients. Epstein Barr virus itself induces expression of the low affinity IgE receptor, CD23,¹⁷ which in turn stimulates IgE synthesis.^{18,19} Among HIV-seronegative renal transplant recipients, increased serum IgE levels have also been associated with disseminated cytomegalovirus infection.²⁰

The data in this study demonstrate that the presence of hepatitis B surface antibody in HIV-seropositive patients, indicating prior infection with hepatitis B, is significantly associated with elevated serum IgE levels. It is surprising that only 44% of the injection drug users in this study were hepatitis B

surface antibody positive. Some groups have reported a significant decline in hepatitis B cases in injection drug users after introduction of needle exchange programs.²¹ In this small study, we did not confirm our preliminary findings that injection drug users had higher serum IgE levels than non-injection drug users, probably due to the sample size. Drug use alone is probably not responsible for increased serum IgE levels in HIV-seropositive subjects since we previously determined that median serum IgE levels in HIV seronegative injection drug users are 20.2 IU/mL (unpublished observations), which are similar to those reported in the general population.

IgE synthesis is determined by a complex interplay between T and B lymphocytes and associated cytokines.²² Increased serum IgE levels in HIV infection may be attributed to HIV infection itself, to past or current infection with hepatitis B, or to other allergens. Direct stimulatory effects of HIV itself and/or other HIV associated viruses, such as cytomegalovirus, on IgE production may also contribute to increased serum IgE levels in HIV infection.¹⁴ We previously reported that HIV-infected children with disseminated cytomegalovirus infection had elevated serum IgE levels.²³ In addition, viruses may enhance IgE-mediated histamine release from lung basophils, and antigen-induced IgE-mediated inflammatory responses may play a role in the pathogenesis of viral diseases, including hepatitis B virus and HIV infection.²⁴

Coinfection with hepatitis B may influence HIV-related disease progression.^{6,25} Additional studies are needed to determine whether coinfection with hepatitis B virus is a cause of increased serum IgE levels in persons with HIV infection and whether it is associated with activation of HIV. The inclusion of HIV-seronegative injection drug users with and without prior hepatitis B infection is important in future studies to determine the association of IgE dysregulation with HIV infection, hepatitis B virus, and drug use.

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