Original paper

The demographics of autoimmune hepatitis in human immunodeficiency virus-infected patients: a United States cross-sectional study

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Abstract

Introduction: Autoimmune hepatitis (AIH) is a chronic inflammatory condition of the liver with increasing global prevalence. However, no epidemiological data exist for AIH in human immunodeficiency virus (HIV)-infected patients.

Aim: To determine the demographics and comorbid conditions associated with AIH among HIV-infected individuals in the United States.

Material and methods: The United States National Inpatient Sample database was used to identify HIV hospital encounters in 2012–2014. The encounters were then classified into 2 groups based on a concomitant primary diagnosis of AIH. Primary outcomes included the demographics and comorbid conditions of AIH among HIV-infected patients. Secondary outcomes assessed the independent predictors of AIH.

Results: A total of 48,3310 patients with an HIV diagnosis were included. The estimated AIH prevalence was 52.8/100,000 HIV hospital encounters. The female gender was more likely to have AIH with an odds ratio (OR) of 1.82; 95% confidence interval (CI) 1.42–2.32, $p < 0.0001$. The age intervals of 35–50 and 51–65 years had higher odds of AIH 110 (43.1%) and 115 (45.1%) with OR = 1.30; 95% CI: 1.02–1.67, $p = 0.03$ and OR = 1.34; 95% CI: 1.05–1.71, $p = 0.02$, respectively. African American and Hispanic races were more commonly affected. Moreover, HIV-infected patients with AIH had a higher risk of having elevated transaminases, long-term steroid use, rheumatoid arthritis, and ulcerative colitis.

Conclusions: This study illustrates that the estimated prevalence of AIH in HIV-infected patients in the United States is 52.8/100,000. AIH in HIV-positive individuals has a predilection for the female gender and African American and Hispanic races, and shows a higher correlation with rheumatoid arthritis and ulcerative colitis.

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory hepatic condition. It is characterized by the detection of autoantibodies, elevated serum globulin levels, and histological findings related to interface hepatitis [1]. It can involve any age group, gender, or ethnicity. The spectrum of acute or chronic clinical presentation can vary from asymptomatic disease to patients presenting with abnormal liver biochemical tests, acute hepatitis, acute liver failure, or liver cirrhosis [2]. While certain diagnostic criteria are available, AIH is predominantly diagnosed clinically. The global epidemiological distribution of this disease shows significant heterogeneity, but the estimated incidence is increasing in current times [3]. Hurlburt *et al.* reported an AIH point prevalence of 42.9/100,000 in Alaska Natives [4]. In their large popu-

lation-based national study, Tunio *et al*. estimated the AIH prevalence to be 31.2/100,000 in the United States [5]. However, the demographics of AIH have not been systematically studied in a subset of other clinically important medical conditions, including human immunodeficiency virus (HIV) infection.

HIV infection exposes patients to several serum abnormalities in addition to the immunocompromised status. Polyclonal hypergammaglobulinaemia is a frequently encountered serum abnormality in these patients [6, 7]. Furthermore, HIV-associated immune dysregulation may also cause a variety of autoimmune and systemic clinical conditions [6–8]. HIV infection causes immune activation that persists despite antiretroviral therapy (ART). Several clinical trials have shown that ART reduces the inflammatory markers (interleukin 6, D-dimer, and C-reactive protein) but does not normalize their levels [9, 10]. The underlying pathogenesis of this persistent immune activation and inflammation is poorly understood, but viral persistence and microbial translocation from the gastrointestinal tract are thought to play an important role [11]. Virot *et al.* identified the concurrent occurrence of 36 different types of autoimmune diseases in their analysis of 5186 HIV-infected adults [12]. The autoimmune diseases included immune thrombocytopenic purpura, HIV-associated myositis, sarcoidosis, neurological disorders such as Guillain-Barre syndrome and myasthenia gravis, autoimmune thyroid diseases, autoimmune haemolytic anaemia, systemic lupus erythematosus, rheumatoid arthritis, and AIH [12].

AIH during HIV infection has rarely been recognized and existing literature remains scarce [13, 14]. It has been mainly reported during immune reconstitution [15] or immunovirological control with ART [1]. It is notable that no epidemiological data exist on AIH in HIV-infected patients in the United States [14]. Due to the increasing prevalence and disease burden, we aimed to study AIH in HIV-infected patients using a large population-based database. To our knowledge, this is the first clinical study discussing the demographic characteristics and comorbid conditions associated with AIH in HIV-infected adults. This study carries paramount clinical importance in understanding AIH demographics in HIV patients. It will enable clinicians to create community awareness regarding this important association, which could be increasingly recognized in recent times.

Aim

The objectives of this study were to describe the demographics and comorbid conditions of AIH among HIV-positive hospitalized patients from a large population-based database. We also aim to assess the independent predictors associated with AIH in these patients.

Material and methods

Data source

The National (Nationwide) Inpatient Sample (NIS) database is a part of the Healthcare Cost and Utilization Project (HCUP) developed for US regional and national estimates of inpatient utilization, access, charges, quality, and outcomes. Unweighted, it has data pertaining to over 7 million hospitalizations annually. Weighted, it has more than 35 million hospital stays yearly. This database contains information about patient demographic characteristics (e.g. age, sex, race, median household income for ZIP code, etc.), hospital characteristics (e.g. urban, rural, teaching, or non-teaching), expected payment source, total hospital visit charges, hospital length of stay, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic and procedural codes.

Study population and inclusion criteria

This study included hospitalizations with an HIV diagnosis (ICD-9 codes: 042, 079.53, 795.71, and V08) between 2012 and 2014. We then identified HIV-infected patients with a concurrent primary diagnosis of AIH (ICD-9 code: 571.42). In HIV-infected patients admitted for AIH, the code for AIH was indicative of the primary diagnosis in the administrative NIS database. Therefore, in the group of patients with AIH, it did not indicate the history of AIH in HIV patients; rather, it was the discharge diagnosis in respective hospitalizations. Notably, HIV infection was already diagnosed in this group of patients, which was crucial for the scientific worth of this study. The comorbid conditions of AIH were identified in HIV-infected individuals using ICD-9 codes; nonspecific elevation of levels of transaminase (790.4), long-term use of steroids (V58.65), chronic lymphocytic thyroiditis/autoimmune thyroiditis (245.2), celiac disease (579.0), and rheumatoid arthritis (RA) (714.0, 714.2, 714.30-714.330), etc.

Study outcomes and variables

The primary outcomes were to determine the demographics and comorbid conditions of AIH among HIV-infected patients. The secondary outcome was to calculate the independent predictors associated with AIH in HIV-infected patients. Multiple confounders were identified and accounted for in the analysis like age, sex, race, median household income, payer source, and comorbid conditions.

Study analysis

The analysis was conducted using the Statistical Package for the Social Sciences 23 (SPSS). The NIS database was weighted through the discharge-level weight variable (DISCWT). Categorical factors were compared with χ^2 tests. *P*-values less than 0.05 were considered statistically significant. Multivariable logistic regression was performed to identify independent variables associated with AIH in HIV-infected patients. This study did not require the approval of the institutional review board panel because the NIS-HCUP database does not contain any patient identifiers.

Results

A total of 48,3310 patients with a diagnosis of HIV were included in the study. Notably, a total of 255/48,3310 patients had AIH. The AIH prevalence was estimated to be 52.8 per 100,000 hospitalized HIV-infected patients. The female sex had higher odds of having AIH, with an odds ratio (OR) of 1.82; 95% confidence interval (CI) 1.42–2.32, $p < 0.0001$. The age interval 35–50 and 51–65 years had higher odds of AIH 110 (43.1%) and 115 (45.1%) with OR = 1.30; 95% CI: 1.02–1.67, $p = 0.03$ and OR = 1.34; 95% CI: 1.05–1.71, $p = 0.02$ respectively. Similarly, the median household

Table I. Demographic factors of HIV-infected patients

Characteristic	Autoimmune hepatitis	No autoimmune hepatitis	*P*-value
Age intervals [years]:			
0–17	*	1910 (0.4%)	–
18–35	25 (9.8%)	91,045 (18.8%)	
36–50	110 (43.1%)	177,910 (36.8%)	
51–65	115 (45.1%)	183,660 (38%)	
> 65	*	28,500 (5.9%)	
Sex:			
Male	130 (51%)	315,835 (65.4%)	< 0.0001
Female	125 (49%)	167,165 (34.6%)	
		Missing 55	
Race/ethnicity:			
White	40 (16.3%)	135,130 (28.7%)	0.0001
Black	130 (53.1%)	252,700 (53.7%)	
Hispanic	75 (30.6%)	58,470 (12.4%)	
Asian or Pacific Islander		3220 (0.7%)	
Native American		1700 (0.4%)	
Other	Missing 10	19,640 (4.2%)	
		Missing 12195	
Median ZIP code income quartile:			
0–25%	65 (27.7%)	199,615 (50.1%)	0.0001
26–50%	95 (40.4%)	90,170 (22.7%)	
51–75%	40 (17%)	67,205 (16.9%)	
76–100%	35 (14.9%)	41,070 (10.3%)	
	Missing 20	Missing 84,995	
Primary payer:			
Medicare	90 (35.3%)	156,630 (32.5%)	< 0.0001
Medicaid	70 (27.5%)	188,405 (39.1%)	
Private insurance	70 (27.5%)	78,095 (16.2%)	
Self-pay	*	38,610 (8%)	
No charge	–	4990 (1%)	
Other	15 (5.9%)	15,425 (3.2%)	

Less than 10 cases not shown and are marked with an asterisk (*).

income 26–50th percentile showed higher odds of AIH OR = 2.59; 95% CI: 2.01–3.34, $p < 0.0001$. Medicaid insured patients had lower odds of AIH with OR = 0.59; 95% CI: 0.45–0.78, $p < 0.0001$. Private insured patients showed higher odds of AIH with OR = 1.96; 95% CI: 1.49–2.58, $p < 0.0001$. The African American race was the most common among AIH patients (Table I).

HIV-infected patients with AIH had a higher risk of having elevated transaminases, long-term use of steroids, rheumatoid arthritis (RA), and ulcerative colitis (UC). HIV patients with AIH had lower odds of smoking. There was no statistically significant difference in alcohol consumption, celiac disease, autoimmune thyroiditis, chronic hepatitis B, and chronic hepatitis C in HIV patients with and without AIH (Table II).

The multivariable regression analysis was conducted to estimate independent variables for AIH in HIV-infected patients. The variables found to independently raise the risk of having AIH included age range 51–65 years, female sex, African American and Hispanic ethnicities, median household income 26–50th percentile, Medicare insurance, and other hospital charges. The comorbidities associated with a higher risk of AIH in HIV patients were elevated transaminases, RA, and UC. The statistically significant factors associated with lower AIH chances in HIV-infected patients were age range 36–50 years, private insurance, and smoking. Independent AIH predictors in HIV patients are summarized in Table III.

Discussion

AIH is a chronic inflammatory condition of the liver, the precise aetiology of which remains unknown. The circulating autoantibodies and high serum globulin levels are hallmarks of this disease [16]. One plausible explanation for AIH pathophysiology implicates environmental factors in genetically predisposed individuals [17]. These genetic factors include self-antigen tolerance loss, cytotoxic T-cell hyperresponsiveness, and autoantibody formation against hepatic antigens that cause necrosis of hepatocytes and liver parenchymal cells [18]. Notably, the pathogenesis of AIH in HIV-infected patients remains poorly understood [13]. The possible causal mechanism could be related to defective CD4 T-cells, contributing to autoimmunity in HIV [8]. Furthermore, dysfunctional B-cells induced by chronic persistent HIV viraemia increase the number of plasmablasts, which may also be considered to play a pathogenetic role [7].

In this large nationwide study on the characteristics of AIH patients among HIV individuals, we found that AIH was more common in women. This finding is comparable to the results reported in existing medical literature [19]. Genetic risk factors may be one reason, because women had a higher prevalence of non-DRB1*0401 DR4 alleles than men [20]. Kia *et al.* published a case series of AIH in HIV-infected patients, which included 4 women and 1 man, all of whom were African Americans [21]. The explanation behind the racial disparity of AIH remains largely unclear. These racial predilections may also be attributed to the differences in the genetic risk factors.

This study found that AIH usually occurred in the middle-aged population group, with a higher number of AIH individuals aged 51–65 years. In comparison to the series of cases involving 13 HIV-infected AIH patients, 46% and 85% developed AIH at ages below 40 and 50 years, respectively [13]. A population-based study conducted for AIH in New Zealand found that 72% of cases reported after 40 years of age, with the peak age of presentation from 60 to 70 years [22]. Therefore, the

Table II. Comparison of morbidity between HIV-infected patients with and without autoimmune hepatitis

Factor	Autoimmune hepatitis	No-autoimmune hepatitis	Odds ratio	*P*-value
Elevated transaminases	15 (5.9%)	6595 (1.4%)	4.52 (2.68–7.61)	0.0001
Long-term use of steroids	15 (5.9%)	4085 (0.8%)	7.33(4.35–12.36)	0.0001
Smoking	35 (13.7%)	147,845 (30.6%)	0.36 (0.25–0.51)	0.0001
Alcohol	10 (3.9%)	23,660 (4.9%)	0.80 (0.42–1.49)	0.47
RA	15 (5.9%)	2470 (0.5%)	12.16 (7.21–20.52)	0.0001
Celiac disease	0	190 (0.0)	–	0.75
UC	*	1845 (0.4%)	5.22 (2.15–12.66)	0.0001
Autoimmune thyroiditis	0	95 (0.0)	–	0.82
Type 1 DM	0	3730 (0.8%)	–	0.16
Chronic hepatitis B	*	8625 (1.8%)	1.1 (0.45–2.67)	0.83
Chronic hepatitis C	25 (9.8%)	36,510 (7.6%)	1.33 (0.88–2.01)	0.18

RA – rheumatoid arthritis, UC – ulcerative colitis, DM – diabetes mellitus. Less than 10 cases not shown and are marked with an asterisk (*).

Table III. Multivariable logistic regression analysis of factors associated with autoimmune hepatitis in HIV-infected patients

Factor	Odds ratio	95% confidence interval	*P*-value
Age [years]:			
0–17	0.000	0.000	0.99
18–35	1.86	0.70–4.96	0.21
36–50	0.23	0.09–0.57	0.001
51–65	4.30	1.74–10.61	0.002
> 65	R		
Sex:			
Female	2.00	1.55–2.59	0.0001
Race:			
White	R	1.27–2.48	0.001
Black	1.77	3.18–6.63	0.0001
Hispanic	4.59	0.000	0.99
Asian or Pacific Islander	0.000		
Native American	0.000	0.000	0.99
Other	0.000	0.000	0.96
Median ZIP code income quartile:			
0–25%	0.81	0.56–1.16	0.24
26–50%	2.63	1.87–3.69	0.0001
51–75%	1.37	0.91–2.07	0.14
76–100%	R		
Primary payer:			
Medicare	2.34	1.21–4.55	0.01
Medicaid	1.28	0.65–2.50	0.47
Private insurance	0.29	0.15–0.56	0.0001
Self-pay	R		
No charge	0.000	0.000	0.98
Other	3.71	1.66–8.28	0.0001
Elevated transaminases	4.83	2.85–8.17	0.0001
Smoking	0.40	0.28–0.58	0.0001
Alcohol	1.10	0.58–2.08	0.77
RA	8.75	5.13–14.92	0.0001
Celiac disease	0.000	0.000	0.99
UC	5.45	2.23–13.30	0.0001
Autoimmune thyroiditis	0.000	0.000	0.99
Type 1 DM	0.000	0.000	0.98
Chronic hepatitis B	1.14	0.47–2.78	0.78
Chronic hepatitis C	1.31	0.86–1.99	0.21

RA – rheumatoid arthritis, UC – ulcerative colitis, DM – diabetes mellitus.

age results of our study were comparable to AIH in the general population of New Zealand.

HIV patients with AIH had higher risks of elevated transaminases in this study. In HIV-infected individuals, elevated liver enzymes are typically associated with chronic viral hepatitis, infiltrative liver disease, hepatic steatosis, drug-induced liver damage, and AIDS cholangiopathy. Given the nature of HIV infection-related immunosuppression, autoimmune diseases are not frequently considered in this population, which may have a major effect on the management and prognosis of these disorders [23]. Therefore, the differential diagnosis of elevated liver enzymes should include AIH, which is an unusual but potentially treatable clinical entity in HIV-infected individuals.

In accordance with the medical literature on AIH in the general population, HIV-infected patients with AIH have also been found to have a higher correlation with 2 autoimmune diseases, including UC and RA [24, 25]. Unlike previous clinical trials, our study did not indicate a higher correlation of AIH with autoimmune thyroiditis, celiac disease, and type 1 diabetes mellitus [25, 26]. Concurrent autoimmune disorders have been shown to occur in 22% to 34% of patients with AIH [24]. It has been associated with some HLA antigens like HLA-A11, DRB1*04, and DRB4*01. It remains unclear why there is no statistically relevant correlation between AIH and autoimmune thyroiditis, celiac disease, and type 1 diabetes mellitus.

There are no specific recommendations for the treatment of HIV-infected AIH patients [13]. Based on data from case studies, AIH is typically handled in the same manner as non-HIV patients. In accordance with this, our research also showed more long-term use of steroids in HIV-infected patients with AIH. Prednisone monotherapy or combination treatment with azathioprine is the first-line therapy. HIV patients with AIH should be treated with immunosuppresives as these drugs minimize the 2-year mortality rate from 34% to 14% in the AIH patients without HIV infection [27]. AIH patients without cirrhosis of the liver may have a survival comparable to that of the general population [28].

The NIS database has been used for this analysis, which has its own limitations. We could not quantify the association between beginning of ART and developing AIH. Because NIS is an administrative database, it can have coding inaccuracies. This database has only ICD-9 codes available for the liver biopsy procedures and not for the results. Consequently, histopathology findings were not available. Other essential data missing from the NIS database included HIV viral load, duration and acuity of HIV disease, types of care obtained, and compliance with the medical management. However, this research has merits, which included a large sample population that was obtained nationally across the United States. Thus, the sample size was larger than hospital-funded research projects, and it helped to represent a national trend of AIH even though it remains an extremely rare condition among HIV-infected patients. The increased burden of AIH in HIV-infected individuals than general population warrants prospective, controlled studies.

Conclusions

This study illustrates that AIH should be added to the list of differential diagnosis of elevated transaminases in HIV-infected individuals. AIH in HIV infection more commonly involves the female gender and the African American and Hispanic races. The gender and the racial gap may be due to variations in genetic risk factors. HIV individuals with AIH also demonstrate a higher correlation with 2 autoimmune disorders – UC and RA. This study may prove the forerunner in designing population-based prospective randomized clinical trials to establish the causal relationship between ART and AIH. The impact of immunosuppressive therapy on HIV disease should also be meticulously evaluated.

Conflict of interest

The authors declare no conflict of interest.

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