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Autoimmune Hepatitis in Patients with Human Immunodeficiency Virus Infection

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Systematic Review and Meta-Analysis

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Autoimmune hepatitis in patients with human immunodeficiency virus infection

A systematic review of the published literature

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Abstract

Background: Liver disease in patients with HIV is common and typically has complex and multifactorial presentations that represent a major cause of morbidity and mortality. Autoimmune hepatitis (AIH) is rarely reported in patient with HIV and the disease course and clinical outcomes for treatment have not been well characterized. We are aiming to determine the patient characteristics, disease prevalence, and treatment outcomes from published articles of patients with HIV and AIH.

Method: A systematic search of PubMed, Web of Science, and Google Scholar through February 20th, 2019 identified 15 studies that reported the outcomes of AIH in patients with HIV. Because of the small sample sizes and skewed distributions, resampling tests of mean differences using permutation distributions (MAXn = 10,000 permutations) were utilized; analyses were performed using R (v. 3.5.1). Categorical differences were calculated using Fisher exact test for odds ratio = 1 (equal odds), and Cramer V was calculated for effect size; analyses were completed in SPSS (v. 25).

Results: By reviewing 15 studies reporting a total of 35 patients with AIH and HIV, male patients were found to have significantly higher aspartate transaminase and alanine transaminase levels at time of diagnosis. No other significant findings identified. The CD4 count and viral load did not show significant correlation with AIH diagnosis or its prognosis. All patients but one who presented with severe immune deficiency and responded to highly active anti-retroviral therapy received immunosuppressive treatment without side effects and achieved remission except 2 lost to follow-up and 3 expired.

Conclusion: Although rare, but AIH can develop in patients with HIV and physicians should consider it in the differential diagnosis for HIV patients presented with abnormal liver function tests, especially after excluding hepatitis C virus and drug-induced liver injury.

Patients with immune deficiency disorders who present with AIH can be treated safely with steroid either as monotherapy or in combination with another immune suppressant therapy.

Abbreviations: AIH = autoimmune hepatitis, ALT = alanine transaminase, ANA = antinuclear antibodies, anti-LC1 = anti-liver cytosol type 1, anti-LKM1 = anti-liver/kidney microsome type 1, ASMA = anti-smooth muscles antibodies, AST = aspartate transaminase, HAART = highly active anti-retroviral therapy, HIV = Human immune deficiency virus.

Keywords: autoimmune hepatitis, HIV infection

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1. Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by the presence of circulating autoantibodies such as anti-nuclear antibodies (ANA), anti-smooth muscles antibodies (ASMA), anti-liver/kidney microsome type 1 (anti-LKM1), or anti-liver cytosol type 1 (anti-LC1) with hypergammaglobulinemia and typical histological changes like interface hepatitis, plasmacytic infiltrates, and regenerative liver cell rosettes.[1–3] AIH can present at any age, ethnic group, or sex with a female predominance.[4,6] The exact etiology is unknown but proposed to be caused by an environmental trigger associated with defective immune tolerance mechanism in a genetically predisposed individual. This elicits a T-cell-mediated immune reaction targeting hepatocytes leading to progressive inflammation and injury that can end with liver cirrhosis.[4,5] AIH has a variety of clinical phenotypes; therefore, it is included in the differential diagnosis for patients with abnormal liver biochemical tests, acute hepatitis, cirrhosis, or acute liver failure.[7] It may present as either an acute or chronic disease with a fluctuating pattern.[8,9] However, the spectrum of presentation also includes asymptomatic patients.

Since the first description of human immunodeficiency virus (HIV) in 1981, there have been multiple advances in the diagnosis and management of the disease, which have directly affected its prevalence and prognosis. In the anti-retrovirus therapy era for HIV infection, liver diseases are considered one of the most common causes of non–AIDS-related mortality in this population with HIV. This is most commonly as a result of chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infection, medication-related hepatotoxicity, alcohol abuse, or nonalcoholic fatty liver.[3,17] According to the Centers for Disease Control and Prevention (CDC), there have been 1.1 million adults aged 13 years and above living with HIV in the United States with 38,500 estimated new cases annually.[10]

Chronic infection with HIV is characterized by a steady decline in CD4+T-cell count in proportion to the viral burden resulting in a progressive waning of humoral immunity. This also leads to stimulation of B-Cell proliferation and increased immunoglobulins' production a proportion of which may be defective. This immunological dysregulation greatly increases the risk for the development of autoimmune diseases like AIH.[11,12]

Herewith we are providing a systematic review of the available literature on this topic of AIH in HIV patients. With this review, we aim to characterize this population, discuss the patterns by which AIH and HIV affect one another in terms of severity, prognosis, and treatment.

2. Method

We performed a systematic review of available literature on PubMed, Web of Science, and Google Scholar using the words "autoimmune hepatitis in human immune deficiency virus," "AIH in HIV," "Autoimmune diseases in HIV" to extract published articles from January 1st 2000 up to February 20th, 2019 identifying 15 literatures that reported the outcomes of AIH in a total of 35 patients with HIV. Only studies with a liver biopsy-confirmed diagnosis were included in concordance with the AIH group revised criteria. All studies included were written in English except one that was translated from French using Google translate.

An institutional review board approval was not necessary as this study is systematic review of literature and meta-analysis.

Most studies resulted in very limited information, with several single-case reports. Therefore, it was not possible to develop a traditional meta-analytic approach to combining results, and data were combined using sample-size weights for analyses. Because of the small sample sizes and skewed distributions, resampling tests of mean differences using permutation distributions (MAXn = 10,000 permutations) were utilized; these analyses were performed using R (v. 3.5.1). Categorical differences were calculated using Fisher exact test for odds ratio = 1 (equal odds), and Cramer V was calculated for effect size; these analyses were completed in SPSS (v. 25; SPSS Inc, Chicago, IL).

3. Results

Fifteen articles reporting a total of 35 patients with AIH and HIV were included (Table 1). Twenty-six (74.2%) were females and 9 (25.8%) were males with a mean age of 45.7 years and 38.5 years, respectively.

The mean CD4 count at time of diagnosis was 534.85 cells/mm^3 for females and 533.78 cells/mm^3 for males and most cases developed AIH with undetectable HIV viral load except 7 cases had elevated viral load with mean of 61,693 copies/mL at the time of diagnosis and 2 cases with unreported viral load. HCV coinfection was reported in 5 cases (14.2%) and HBV coinfection in 2 cases (5.7%) (Table 2). Other autoimmune diseases coexisted in 6 patients (17.1%) with vitiligo in 1 case, lupus in 2 cases, and Graves disease in 2 cases and 1 case with myasthenia gravis.

Males had significantly higher alanine aminotransferase (ALT; 751.89 U/L vs 181.04 U/L, $P = .035$) and aspartate aminotransferase (AST; 751.89 U/L vs 198.16 U/L, $P = .037$) than females. Both sexes have similar alkaline phosphatase levels (Table 2).

Liver biopsy was performed to confirm the diagnosis of AIH in all patients using the revised criteria of the International Autoimmune Hepatitis group (IAH+IHG) score of >15[3,13] (Table 3).

All patients were on highly active anti-retroviral therapy (HAART) therapy at time of diagnosis with 15 patients (42.8%) receiving efavirenz, emtricitabine, and tenofovir and 4 patients on unknown regimen at the time of diagnosis.

Table 1

List of included literature.

Author	Date of study	Number of patients
Kia et al[1]	2017	5
Zoboli et al[2]	2017	2
Parekh et al[3]	2017	2
German[5]	2004	1
Puius et al[19]	2006	3
Vispo et al.[20]	2008	1
Caplan[21]	2013	1
O'Leary et al[25]	2008	1
Daas et al[26]	2011	1
Murunga et al[27]	2014	9
Cazanave et al[28]	2005	1
Wan et al[29]	2009	4
Ofori et al[30]	2017	2
Hagel et al[31]	2012	1
Coriat et al[32]	2008	1

Table 2

Summary of the results.

Continuous variables

	Sex	n	Mean	SD	*P*
Age	Female	21	45.71	10.91	.129
	Male	8	38.50	11.26	
CD4 Count at Dx	Female	26	534.85	286.18	.992
	Male	9	533.78	247.57	
AST	Female	25	198.16	300.20	.037
	Male	9	751.89	1209.87	
ALT	Female	26	181.04	307.27	.035
	Male	8	853.22	1549.79	
ALP	Female	26	81.87	140.90	.916
	Male	8	75.45	80.90	
Period of follow-up	Female	20	8.18	12.49	.653
	Male	7	10.79	8.62	

Categorical variables

	Sex	No (%)	Yes (%)	Cramer V	*P*
HCV coinfection	Female	19 (82.6)	4 (17.4)	0.035	>.999
	Male	6 (85.7)	1 (14.3)		
HBV coinfection	Female	23 (100.0)	0 (0.0)	0.445	.060
	Male	6 (75.0)	2 (25.0)		

ALP = alkaline phosphatase, ALT = alanine transaminase, AST = aspartate transaminase, HBV = hepatitis B virus, HCV = hepatitis C virus.

Table 3

Simplified criteria of international autoimmune hepatitis group 2008.

		Points
Autoantibodies	ANA, SMA, OR LKM >1: 40	1
	ANA, SMA, OR LKM >1: 80 SLA/LP-positive (>20 U)	2
Ig G	Upper limit of normal	1
	>1.10× the upper limit of normal	2
Liver histology	Compatible with AIH Chronic hepatitis with lymphocytic infiltrations without features considered typical	1
	Typical for AIH interface hepatitis; lymphocytic/lymphoplasmacytic infiltrates in the portal tracts Emperipolesis: active penetrations by one cell into and through larger cell hepatic rosette formation	2
Absence of viral hepatitis	No	0
	Yes	2
Interpretation	Points >6: probable AIH Points >7: definite AIH	

AIH = autoimmune hepatitis, ANA = anti-nuclear antibodies, ASMA = anti-smooth muscles antibodies, anti-LKM1 = anti-liver/kidney microsome type 1, SLA/LP = Soluble liver antigen/liver-pancreas.

All cases were treated successfully with immunosuppressants including steroid as monotherapy or tapered steroid with addition of other immunosuppressive (azathioprine). Two cases were exception as 1 case presented with severe immune deficiency and responded to HAART and 1 case refused treatment. Thirty patients had complete remission, 2 cases lost to follow–up, and 3 patients died (1 patient because of fulminant liver failure, 1 because of CMV viremia, and 1 because of Burkitt lymphoma). The range of follow-up was 1 to 48 months with an average of 9.48 months (Table 2).

4. Discussion

AIH is a rare entity of liver disease with specific serological and histological findings characterized by insidious onset of immunological reaction against hepatocytes causing progressive inflammation and fibrosis leading to liver cirrhosis.[5] International Autoimmune Hepatitis Group scoring system that was developed originally in 1999 has been beneficial in diagnosing this condition and a more simplified version of this scoring system has been adopted in 2008 incorporating laboratory results and histological findings on liver biopsy (Table 3).[3,13] Treatment usually includes high-dose steroids as monotherapy or low-dose steroids in combination with immunosuppressants (eg, azathioprine). AIH in patients with established HIV infection has been rarely reported in the literature and the disease course, prognosis, and response to therapy have not been well documented.[5]

Elevated liver enzymes in patients infected with HIV are usually related to viral hepatitis, alcoholic liver disease, drug-induced toxicity, metabolic abnormalities, immune-mediated cholestatic disease, or hereditary disorders. Given the nature of HIV infection and its effect on the immune system, autoimmune diseases have been infrequently described in such patient populations and even less are cases describing HIV patients with diagnosis of AIH, which can have significant consequences on its management and prognosis.[2]

Initiation of HAART in HIV or AIDS patients with low CD-4 count has been associated with exacerbation of preexisting immunological conditions such as sarcoidosis and thyroiditis as part of systemic inflammatory response syndrome (SIRS). AIH has been reported as a possible result of SIRS [22]; however, most of the patients in our study were already on HAART with well-controlled HIV at time of diagnosis of AIH.

Full evaluation of suspected cases of AIH in HIV patients starts with a detailed history, evaluation of medication regimen, alcohol consumption, and sexual history. It should also include evaluation of conventional serological markers and liver biopsy for histological evaluation.[4,13]

Initial laboratory evaluation of suspected cases includes ANA, ASMA, anti-LKM1, and anti-LC1. Liver biopsy is recommended early for diagnosis. Typical findings include prominent interface with zone 1 hepatitis or irregularly distributed and relatively intense portal infiltrate with either periportal or paraseptal interface hepatitis. Other histopathological findings can be evaluated but are usually less specific and less pathognomic. Based on serological findings, AIH is usually classified into 2 types. Type I is characterized by presence of ANA and ASMA and constitutes 80% of AIH cases. Type II is characterized with presence of anti-LKM1 and anti-LC1 and is mostly found in children.[1–4,14,15]

The decision to start treatment for patients with AIH in general depends on the severity of the clinical presentation (Table 4).[4] It includes starting high-dose corticosteroid as a single agent or low-dose steroids in conjunction with other immunosuppressants, such as azathioprine. Later regimen can be tapered down

Table 4

Indication to start treatment in patient with AIH.

Absolute	Relative	none
• Serum AST >10-fold ULN	• Symptoms (fatigue, arthralgia, jaundice)	• Asymptomatic with normal or near normal serum AST and gamma globulin levels
• Serum AST >5-fold ULN and gamma globulin level >2-fold ULN	• Serum AST and/or c globulin less than absolute criteria	• Inactive cirrhosis or mild portal inflammation (portal hepatitis)
• Incapacitating symptoms	• Interface hepatitis	• Severe cytopenia
	• Osteopenia, emotional instability, hypertension, diabetes, or cytopenia (white blood cell counts $<2.5\times10^9$ cells/L or platelet counts $<50\times10^9$ cells/L)	• Vertebral compression, psychosis, brittle diabetes, uncontrolled hypertension, known intolerances to prednisone or azathioprine

AST = aspartate transaminase, ULN = upper limit of normal.

individually to sustain enough suppression. The immunosuppressive dosage appears to be individualized to each patient as different doses of azathioprine were used to achieve sustained immunosuppression ranging from 50 mg daily to 200 mg daily.

Although it is controversial to start patients with chronic HIV on immunosuppressive therapy given the risk of opportunistic infection, worsening of HIV status, or increasing risk of development of malignancies as shown by previous studies that reported increase in Kaposi sarcoma in HIV patients on immunosuppressive drugs,[16,15] it is still recommended to start immunosuppressive treatment to achieve remission and prevent disease progression.[2,3,19,20]

Particular attention is needed to evaluate for possible drug–drug interaction between immunosuppressive medications like azathioprine and antiretroviral medications, as they share common elimination and metabolism pathways such as cytochrome P450 enzyme system or P-Glycoprotein and MRP pathways. These interactions are especially profound with protease inhibitors. Studies done in patients with HIV who are organ transplant recipients showed better drug–drug interaction profile with integrase strand transferase inhibitors.

Our literature of interest did not report a specific interaction associated with the use of maintenance immunosuppressive medications like azathioprine and the HAART regimen.

Some studies mentioned the possibility of triggering AIH by HIV infection or during the immune reconstitution phase after starting the antiretroviral medications and correlated the development of autoimmune diseases to high CD4 count, but no significant correlation was demonstrated with subsequent studies.[1,5,18,23,24]

Our literature review did not show significance in a correlation of CD4 count and HIV viral load in diagnosing AIH or anticipating the severity of illness. AIH is more prevalent in the female population that is aligned with the literature. AST and ALT levels were significantly higher at time of diagnosis in males compared to females. Theoretically, this finding can be explained by hormonal differences or difference in genetic expression. Also, it can be explained by the presence of undiagnosed chronic hepatitis conditions or were incorrect diagnosis with AIH, as drug-induced liver injury can sometimes mimic AIH. Further studies are needed to determine the sex differences in transaminases. Our review supports the current recommendations of treating AIH in patients with HIV with steroids as monotherapy or in conjunction with other immunosuppressants mainly azathioprine.[4]

Author contributions

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