Epidemiological and clinical characteristics of autoimmune hepatitis in Albania

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Abstract

Aim: The prevalence of autoimmune hepatitis (AIH) in Albania is unknown. Our aim was to investigate the epidemiological characteristics, biochemical and immunological features of AIH in Albania.

Methods: Our study included 96 consecutive patients (69% female), newly diagnosed with AIH, hospitalized at the Gastro-Hepatology Service of the University Hospital Center "Mother Teresa" in Tirana, the only academic center in Albania, during 2005-2013. Model for End-stage Liver Disease (MELD) and noninvasive biomarkers of fibrosis: AST to platelet ratio index, platelet count to spleen diameter, AST-to-ALT ratio, the age–spleen-to-platelet ratio index, fibrosis-4 score based on age, ALT, AST and platelet count (FIB-4) were measured for each patient.

Results: The prevalence of AIH was 4.38/100,000 inhabitants. Median and mean age of presentation were 34 years and 47.2±17.5 years for males, and 62 years and 52.6±13.2 years for females. At diagnosis, 62.5% of the patients had cirrhosis and MELD was significantly higher among type 2 than type 1 AIH patients (17.2±8.6 vs. 15.0±6.3, respectively, $p<0.05$). There were 92 patients (96%) who presented with symptoms. Mean values of noninvasive biomarkers did not differ significantly between two types of AIH. Other AI diseases were observed in 28 patients (29%).

Conclusions: AIH is uncommon diseases in Albania. The presence of cirrhosis in the majority of the patients at diagnosis suggests more awareness for this chronic liver disease. In addition, the concomitant autoimmune diseases and family occurrence indicate the role of genetic factors in the development of disease. Prospective studies are needed in the future to evaluate the role of genetic and environmental factors in disease predisposition and improve the diagnostic criteria.

Keywords: *autoimmune hepatitis, diagnosis, epidemiology, non-invasive biomarkers.*

Introduction

Autoimmune hepatitis (AIH) has been defined as an unresolving, predominantly periportal hepatitis, usually with hypergammaglobulinemia and tissue autoantibodies, which is responsive to immunosuppressive therapy in most cases (1). It is a relatively rare disorder, with a preponderance of female patients, that can present at any age (although onset in most cases is after 40 years of age). AIH can be subdivided into two types, based on the type of serum autoantibodies: type 1 AIH, identifiable by antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA), and type 2 AIH defined by antibodies against liver kidney microsomes type 1 (anti-LKM-1) or for anti-liver cytosol type 1 antibodies (2,3). The clinical presentation may be acute, acute severe (fulminant), or asymptomatic; conventional autoantibodies may be absent; centrilobular necrosis and bile duct changes may be present; and the disease may occur after liver transplantation or with features that suggest overlapping disorders. In recent years, several issues have been raised on AIH, related to the clinical utility of the classification of AIH, the impact of sex on disease prognosis and the impact of age at the moment of presentation. Moreover, in the literature, there are few studies on epidemiology data, laboratory findings and clinical presentation at diagnosis of AIH.

To date, the epidemiological and clinical characteristics of autoimmune hepatitis in Albania are unknown. According to the last Albanian National Health Report, the main causes of chronic liver disease in Albania are alcohol consumption and hepatitis B virus chronic infection (4). Therefore, the aim of our study was to investigate the prevalence, biochemical and immunological features as well as clinical characteristics of AIH in Albania, a Mediterranean country with high domestic alcoholic consumption and a hyper-endemic area of hepatitis B virus infection.

Methods

Study population

This was a retrospective study, based on data collected from patient's medical record. During 2005-2013, 96 consecutive patients (69% female), newlydiagnosed with AIH, at the University Service of Gastro-Hepatology, University Hospital "Mother Theresa" in Tirana, the only academic center in Albania, were enrolled for this study. The diagnosis had been based on the clinical, biochemical, immunological and histopathological criteria (5,6). We have excluded the viral hepatitis by serological test, the alcohol and drug related hepatitis by clinical history and other known causes of chronic liver diseases.

Data collection

For each patient, we collected the demographic, clinical, biochemical and immunological data. Also, all patients have undergone ultrasonography and endoscopic assessment. Laboratory data included: aspartate aminotransferase (AST) and alanine aminotransferase (AST) level, platelet count (PLT), serum albumin, total serum bilirubin, gamma glutamyltranspeptidase (GGT), gamma globulin, prothrombin time with international normalized ratio (INR), alkaline phosphatase (ALP), serum creatinine, and immunological features such as antinuclear antibodies (ANA), smooth muscle antibodies (SMA) and antibodies to liver-kidney microsome type 1 (anti-LKM1). Additionally, we calculated the Model for End-stage Liver Disease (MELD) and non-invasive biomarkers of fibrosis: AST to platelet ratio index (APRI), platelet count to spleen diameter (PC/SD), AST-to-ALT ratio (AST/ALT), and the age–spleen-to-platelet ratio index (ASPRI), fibrosis-4 score based on age, ALT, AST and platelet count (FIB-4) (Table 1). MELD score was determined by using the UNOS Internet site MELD calculator (http://www.unos.org/).

Table 1. Formulas of non-invasive biomarkers

Score	Formulas
APRI	{(AST *[U/L])* /ULN) / PLT *[10^9/L]*}× 100
ASPRI	age + spleen size (cm) / PLT (10^9/L)] x 100 Age (years): <30=0; 30-39=1; 40-49=2; 50-59=3; 60-69=4; >70=5
FIB-4	(age [years] x AST [U/L]) / (PLT [10^9/L]) x (ALT [U/L] ^{½})
PC/SD	PLT (10^9/L) / SD (mm)

APRI, AST to platelet ratio index; ASPRI, the age–spleen-to-platelet ratio index; FIB-4, fibrosis-4 score; PC/SD, platelet count to spleen diameter.
ALT, alanine aminotransferase; AST, aspartateaminotransferase; PLT, platelets count; SD, spleen diameter; ULN, upper limit of normal.

Statistical analysis

All categorical data are expressed as numbers (percentage). Chi-square test was used to compare the distribution of sex, type of disease, frequencies of symptoms and other autoimmune disorders between patients with type 1 AIH and type 2 AIH. Conversely, ANOVA test was employed to compare mean values of age, biochemical parameters (platelet count, serum albumin, total serum bilirubin, AST, ALT, GGT, ALP, gamma globulin, prothrombin time, INR, serum creatinine, and ANA, SMA and anti-LKM1). All continues data are expressed as mean value and standard deviation.

All the statistical analyses were conducted in SPSS (Statistical Package for Social Sciences), version 19.0.

Results

During a period of eight years, we diagnosed 96 patients (66 females and 30 males) with AIH; 72 (75%) type 1 AIH and 24 (25%) type 2 AIH. Median and mean age of presentation were 34 years (47.2±17.5) and 62 years (52.6±13.2) for male and

Table 2. Epidemiological data, biochemical and immunological features at presentation in patients with autoimmune hepatitis

Features	All patients (96 patients)	Type 1 AIH (72 patients)	Type 2 AIH (24 patients)	P value*
Gender (female/male); n	66/30	50/22	16/8	0.092
Age (years)	50.7±15.0†	53.8 ±12.6	41.4 ±17.9	**0.001**
AST (UI/l)	120.1±111.7	125.8±125.2	103.2±52.9	0.394
ALT (UI/l)	120.5±128.1	131.1±142.9	88.6±57.1	0.160
ALP (UI/l)	228.9±194.5	215.9±188.9	267.8±210.0	0.260
Bilirubin (mg/dl)	4.3±6.6	4.0±5.9	5.2±8.3	0.439
Gamma GT(UI/l)	224.4±238.5	225.8±258.8	220.1±168	0.919
Gamma Globulin (g/l)	28.9 ±10.2	27.2±8.8	33.8 ±12.5	**0.006**
INR	1.5±0.6	1.3±0.5	2.0±0.9	**0.001**
Albumin (g/dl)	3.3±0.6	3.3±0.6	3.2±0.8	0.735
Creatinine (mg/dl)	1.3±1.8	1.3±2.0	1.1±0.3	0.553
ANA pos; n (%)	66 (68.8)	53 (73.6)	13 (54.2)	0.125
SMA pos; n (%)	54 (56.3)	45 (62.5)	9 (37.5)	**0.029**
anti-LKM1pos; n (%)	22 (22.9)	0 (0.0)	22 (91.7)	**0.001**

*Chi-square test was used for categorical variables; ANOVA was used for continuous variables
†Mean ± SD (all such values).

Note: AIH, autoimmune hepatitis; ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate aminotransferese; INR, international normalized ratio;Gamma GT, gamma glutamyl transpeptidase; ANA, antinuclear antibodies; anti-LKM1, antibodies to liver-kidney microsome type 1; SMA, smooth muscle antibodies.

female, respectively. Median age was significantly higher among type 1 than type 2 AIH patients (53.8 ±12.6 vs. 41.4 ±17.9 years, respectively, p<0.05) (Table 2).

The point prevalence of AIH in 2013 was 4.38/ 100,000 inhabitants.

The main biochemical and immunological features at presentation in patients with autoimmune hepatitis and among patients with type 1 AIH and type 2 AIH are reported in Table 2. There were no differences between patients with type 1 AIH and type 2 AIH regarding mean levels of AST and ALT, ALP, GGT, bilirubin, albumin, and serum creatinine. Conversely, mean value of INR and gamma globulin were significantly higher among patients with type 2 AIH than in those with type 1 AIH (2.0 vs. 1.3 and 33.8 vs. 27.2, respectively; P<0.001). Sixty-nine percent (66/96) of patients had antinuclear antibodies positive, 56% (54/96) smooth muscle antibodies positive and 23 (22/96) antibodies to liver-kidney microsome type 1 positive (Table 2).

On Table 3 we have reported the mean values of AST/ALT, MELD score, ASPRI and FIB-4in patients with type 1 AIH and type 2 AIH at presentation. MELD was significantly higher among type 2 than type 1 AIH patients (17.2±8.6 vs. 14.3±5.2, respectively, p<0.05) while mean values of other non-invasive biomarkers did not differ significantly between two types of AIH (Table 3).

Table 3. Noninvasive biomarkers of liver fibrosis at presentation in patients with autoimmune hepatitis

Variables*	All patients (96 patients)	Type 1 AIH (72 patients)	Type 2 AIH (24 patients)	P value†
MELD	15.0±6.3‡	14.3±5.2	17.2±8.6	**0.046**
APRI	3.0±5.2	3.3±5.9	2.0±1.5	0.265
PL/SD	1437.3±985.1	1430.8±1008.6	1456.5±931.5	0.912
AST/ALT	1.3±0.7	1.3±0.7	1.4±0.6	0.428
ASPRI	16.2±12.9	16.4±13.8	15.6±10.0	0.796
FIB-4	4.9±6.0	5.4±6.6	3.3±3.0	0.131

*MELD, Model for End-stage Liver Disease; APRI, AST to platelet ratio index; PC/SD, platelet count to spleen diameter; AST/ALT, AST-to-ALT ratio; ASPRI, the age–spleen-to-platelet ratio index; FIB-4, fibrosis-4 score based on age, ALT, AST and platelet count.

†ANOVA was used for continuous variables

‡Mean ± SD (all such values)

Ninety-six percent (92/96) of patients presented with symptoms (Table 4). At the moment of presentation 62.5% of patients had liver cirrhosis.86 patients (89.6%) were presented with fatigue. Among other clinical manifestations were: abdominal pain (38.5%), jaundice (19.8%), anorexia (18.8%), joint pain (12.5%) and myalgia (6.3%). Other autoimmune diseases were observed in 28 patients (29%), such as 13 (13.5%) patients with diabetes mellitus, 3 (3.1%) patients with thyroid diseases, etc. (Table 4). Also, six percent (6/96) of patients had the family history for autoimmune diseases.

Discussion

The present study is the first Albanian study which reports the epidemiological and biochemical data of 96 patients with AIH diagnosed to the only tertiary referral center for chronic liver diseases in Albania. We found a female predominance and the incidence seems to be higher to the older age than among younger compare with man. At diagnosis, sixty percent of the patients had already developed cirrhosis and most of them are presented with ascites and/or esophageal varices. Almost 35% of the patients reported to have another autoimmune disease or family history for auto-

Table 4. Frequencies of symptoms and other autoimmune disorders at presentation in patients with autoimmune hepatitis

Variables	All patients (96 patients)	Type 1 AIH (72 patients)	Type 2 AIH (24 patients)	P value*
Fatigue; n (%)	86 (89.6)	64 (88.9)	22 (91.7)	1.000
Joint pain; n (%)	12 (12.5)	6 (8.3)	6 (25)	0.067
Jaundice; n (%)	19 (19.8)	12 (16.7)	7 (29.2)	0.237
Abdominal pain; n (%)	37 (38.5)	30 (41.7)	7 (29.2)	0.338
Myalgia; n (%)	6 (6.3)	2 (2.8)	4 (16.7)	0.033
Anorexia; n (%)	18 (18.8)	16 (22.2)	2 (8.3)	0.225
Other symptoms; n (%)	12 (12.5)	10 (13.9)	2 (8.3)	0.378
Esophageal varices; n (%)	43 (44.8)	34 (47.2)	9 (37.5)	0.910
Ascites; n (%)	32 (33.3)	24 (33.3)	8 (33.3)	1.000
Diabetes mellitus; n (%)	13 (13.5)	11 (15.3)	2 (8.3)	0.595
Thyroid disease; n (%)	3 (3.1)	3 (4.2)	0 (0.0)	0.417
Rheumatoid Arthritis; n (%)	3 (3.1)	3 (4.2)	0 (0.0)	0.571
AI hemolytic anemia; n (%)	1 (1)	0 (0.0)	1 (4)	0.250
Other AI diseases; n (%)	8 (8.3)	6 (8.3)	2 (8.3)	1.000
Family history with AI disease; n (%)	6 (6.2)	5 (7.0)	1 (4.2)	0.813

*Chi-square test was used for categorical variables.

immune disease.

A chronic form of hepatitis in young women was first described by Jan Waldenström in 1950 (7). It was termed "lupoid hepatitis" because of the presence of antinuclear antibodies and lupus erythematosus cells and the association with other autoimmune diseases (8). These findings indicated that the foundation of this disease was a loss of immunological tolerance. Later, the term auto immune hepatitis was introduced by Mackay and colleagues in 1965 when the concept of autoimmunity was acknowledged at an international meeting (9). However, AIH is still considering a rare disease with unknown etiology. Moreover, epidemiological studies in AIH are scarce and therefore autoimmune hepatitis remains a major diagnostic and therapeutic challenge.

There are few studies about AIH prevalence and incidence. On Table 5 we have shown some of these studies. The prevalence of AIH is still gradually increasing. The highest prevalence is noted in North America (Alaska), which are 42.9 per 100.000 people. The European countries own a relatively high prevalence from 10.7 to 23.9 per 100.000 people, with the prevalence of Denmark as the highest. In Asia-Pacific area, New Zealand demonstrated a high prevalence of 24.5 per 100.000, while other countries owned comparatively low prevalence. Women are affected more frequently than men with a sex ratio of around 4:1. In women a bimodal age pattern is usually seen, one in the late teens and one around the menopause but it should be stressed that disease can develop in all age groups and both genders (2,10). In our study, the point prevalence of AIH in 2013 was 4.38/100,000 inhabitants which is lower than in other European Countries.

Table 5. Studies of incidence and prevalence per 100.000 inhabitants of autoimmune hepatitis

Author	Year	Country	Total number of cases	Incidence	Prevalence
Primo et al. (26)	2004	Spain	13	1.37	11.61
Werner et al. (21)	2008	Sweden	473	0.85	10.7
Ngu et al. (27)	2010	New Zealand	138	2.0	24.5
Delgado et al. (28)	2013	Israel	100	0.67	11.0
Gerven et al. (19)	2014	Netherlands	1313	1.1	18.3
Grønbæk et al. (29)	2014	Denmark	1721	1.68	23.9
Bo Hyun et al. (30)	2017	South Korea	4085	1.07	4.82

The clinical manifestation of AIH varies from mild or severe symptoms to fulminant hepatic failure (11). AIH might be unrecognized, because of the large heterogeneity of this disease. There is no existence of a pathognomonic feature in AIH and therefore the diagnosis rests on a combination of immunological, biochemical, and histological features together with exclusion of other liver diseases. AIH should be considered in all patients with liver disease. 40 percent of patients presents with acute hepatitis, characterized by right upper-quadrant abdominal pain, fatigue, jaundice and arthralgia (12). However a fulminant manifestation or a long sub clinical course with only minimal increase of liver enzymes and non-specific symptoms, such as arthralgia or fatigue, may be seen (13-17). Clinical manifestations of AIH may vary among ethnic groups. Non-Caucasian patients (the majority being from African-American descent) had more aggressive disease at initial presentation, lower reaction to immunosuppressive therapy, and worse outcomes, compared to Caucasian patients (11). Higher rates of cirrhosis were found in Hispanic patients *compared to* Caucasian patients, and a trend towards worse survival among Asians (18). In our study, we found that 62.5% of the patients at the moment of presentation have already liver cirrhosis which may suggest the delay of diagnosis.

Other autoimmune diseases are common in up to 40% of AIH patients. They included thyroid disease, rheumatoid arthritis, inflammatory bowel disease and diabetes (20). A recent study demonstrates that celiac disease is more prevalent among AIH patients compared to the general population (19). In addition, AIH may present with cholestatic features that can resemble primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC). Furthermore, the overlap with PSC or PBC has been described in 2%-8% and 10%-20% of patients with AIH, respectively (21-25). In our study, manifestation of other auto-immune disorders and presence of concomitant autoimmune diseases were frequently reported. Therefore, the diagnostic screening for other autoimmune diseases may recommend in patients with AIH.

In conclusion, AIH is an uncommon disease in Albania. The presence of cirrhosis in the majority of the patients at diagnosis suggests more awareness for this chronic liver disease. Therefore, a more liberal attitude towards testing for autoantibodies in patients with impaired liver function should be adopted. In addition, the concomitant autoimmune diseases and family occurrence indicate the role of genetic factors in the development of disease. Prospective studies are needed in the future to evaluate the role of genetic and environmental factors in disease predisposition and improve the diagnostic criteria.

Conflicts of interest: None declared.

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