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Patterns and Outcome of Autoimmune Chronic Liver Diseases in Assiut University Hospital: A Retrospective Study

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ABSTRACT

Background& aim: Autoimmune liver diseases (AILD) are relatively low diseases but their pattern and outcome are still unclear. It includes primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis (AIH). The current study was conducted to assess pattern of AILDs in our locality

Methods: This retrospective study was conducted between 2016 and 2019 in Tropical Medicine and Gastroenterology Department, Assiut University Hospitals. In addition to characteristics of patients, types and outcome of AILDs were registered.

Results: A total of 1750 patients with various chronic liver diseases were identified only 2.9% of those patients had different types of AILDs, as follows: 40 patients had AIH, 6 patients had PSC, and 4 patients had PBC, 80% of them were females.

Conclusion: AILDs are still underappreciated in our community. Patients with unexplained abnormalities in liver functions should be suspected of having such diseases. Future multi-center studies on this topic are necessary.

Keywords: Autoimmune liver diseases, Chronic hepatitis, Autoantibodies, Antinuclear antibodies.

INTRODUCTION

Hepatologists and gastroenterologists are frequently facing different forms of chronic hepatitis; autoimmune liver diseases are one of these forms but in less frequency than other chronic diseases. Immune mediated pathophysiology with formation of different types of autoantibodies is the main accepted, till now, theory about initiation of such diseases [1, 2].

There are different subtypes of AILD include autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC) and overlap syndrome. Raised serum immunoglobulin (IgG) with specific pattern of autoantibodies in a common feature in AILD and help in its prediction and diagnosis [1, 2]. Till now, there is paucity in literature about the accurate frequency of such issue globally. Also, the literature didn't supply a full view about age predication, sex predominance and the course of different subtypes of AILD [3, 4]. The pattern and frequency of AILD also, are not well reported in our locality. As a result, the current study sought to assess the various patterns of AILD in our setting.

PATIENTS AND METHODS

Ethical approval:

The study protocol was approved by the Ethics Review Board of Faculty of Medicine, Assiut University and was conducted according to the declaration of Helsinki. The committee's reference number is 17100051. *Clinicaltrails.gov* ID: NCT03898414. All co-authors have seen and agreed with the contents of the manuscript and there is no conflict of interest to report. We certify that it is not under review at any other publication.

Study setting& design

A retrospective-prospective cross-sectional study was achieved at Tropical Medicine and Gastroenterology Department. The study reviewed the medical records of patients with AILD between 2016 and 2019.

Patient's selection

Any patient with any form of AILD and was admitted to the hospital in the study period was recruited in the study. All other forms of liver diseases were excluded.

The following data were collected

Demographics (age, sex and causes of hospital admission) and physical evaluation were recorded, in addition to, liver function tests, kidney function tests and different autoantibodies panel. Also, different lines of therapy, radiological data and outcome in those patients were recorded. Final diagnoses of AILDs was obtained based on different diagnostic criteria for each type of AILD [5-7].

Statistical analysis

Statistical Package for the Social Science version 20 (SPSS, IBM, and Armonk, New York) was used for data analysis. Continuous data were expressed in the form of mean ± SD and were compared with ANOVA test between different forms of AILDs. Nominal data were expressed in form of frequency (percentage) and were compared by *Chi²*-test. The level of confidence was kept at 95%, hence a P value ≤ 0.05 indicated a significant association.

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RESULTS

Out of 1750 patients were admitted with chronic liver diseases, only 50 (2.9%) patients were diagnosed to have AILD (figure 1).

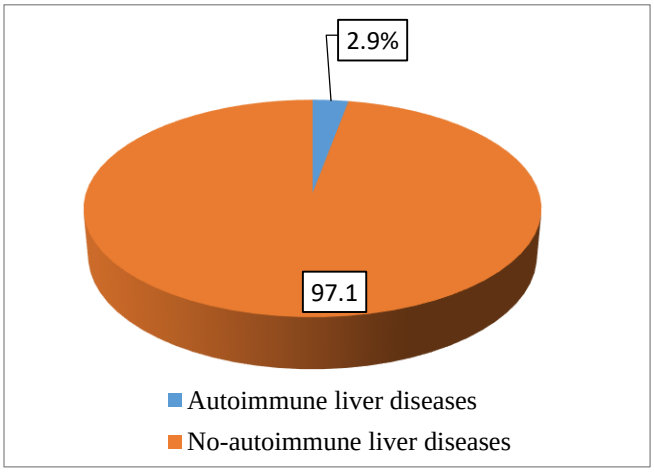

Figure (1): Frequency of autoimmune liver diseases in the current study.

Baseline data of patients with autoimmune liver diseases (table 1):

Mean age of enrolled patients was 37.50 ± 11.05 years with range between 16 and 56 years. With exception of only 9 male patients, all other patients were females. Majority (78%) of patients came from rural areas.

Table (1): Baseline data of patients with autoimmune liver diseases

	N= 50
Age (years)	37.50 ± 11.05
Range	16-56
Age group	
< 20 years	2 (4%)
20-40 years	30 (60%
> 40 years	18 (36%)
Sex	
Male	9 (18%)
Female	41 (82%)
Diabetes mellitus	8 (16%)
Hypertension	5 (10%)
Smoking	2 (4%)
Residence	
Rural	39 (78%)
Urban	11 (22%)

Data expressed as frequency (percentage), mean (SD).

Clinical data of patients with autoimmune liver diseases (table 2):

The most frequent manifestations among enrolled patients were jaundice (92%), fatigue (84%) and abdominal pain (40%). Itching was experienced in 15 (30%) patients.

Table (2): Clinical data of patients with autoimmune liver diseases

	N= 50
Disease duration (years)	2.48 ± 1.55
Range	1-6
Jaundice	46 (92%)
Fatigue	42 (84%)
Itching	15 (30%)
Fever	8 (16%)
Abdominal pain	20 (40%)
Melena	4 (8%)
Hematemesis	4 (8%)
Hepatic encephalopathy	8 (16%)

Data expressed as frequency (percentage), mean (SD).

Laboratory and imaging data of patients with autoimmune liver diseases (table 3):

Only four patients had positive AMA and only other two patients had positive anti-LKMA. Liver biopsy was done in only 11 (22%) patients and all of them had picture suggestive of autoimmune hepatitis.

Table (3): Laboratory and imaging data of patients with autoimmune liver diseases

	N= 50
Hemoglobin (mg/dl)	10.81 ± 1.45
Platelets (ul/10^3)	179.83 ± 6.87
Leucocytes (ul/10^3)	10.45 ± 2.61
INR	1.38 ± 0.38
Bilirubin (mmol/l)	176.73 ± 8.34
Direct bilirubin (mmol/l)	101.26 ± 9.76
Albumin (mg/dl)	30.54 ± 5.26
Aspartate transaminase (U/L)	214.08 ± 8.45
Alanine transaminase (U/L)	204.72 ± 33.45
Alkaline phosphatase (U/L)	260.47 ± 69.13
Immunoglobulin (g/dl)	1.77 ± 0.42
Positive ANA	36 (72%)
Positive ASMA	24 (48%)
Positive AMA	4 (8%)
Positive anti-LKMA	2 (4%)
Hepatomegaly	10 (20%)
Splenomegaly	29 (58%)
Ascites	10 (20%)
Biliary stricture	6 (12%)
Liver biopsy	
Done	11 (22%)
Not done	39 (78%)

Data expressed as frequency (percentage), mean (SD). INR: international randomized ratio; ANA: antinuclear antibody; ASMA: anti-smooth antibody; AMA: anti mitochondrial antibody; LKMA: liver kidney microsomal antibody

Final diagnosis among patients with autoimmune liver diseases (figure 2):

Autoimmune hepatitis was diagnosed in 40 (80%) patients. Six (12%) patients were diagnosed to

have primary sclerosing cholangitis while 4 (8%) patients had primary biliary cirrhosis.

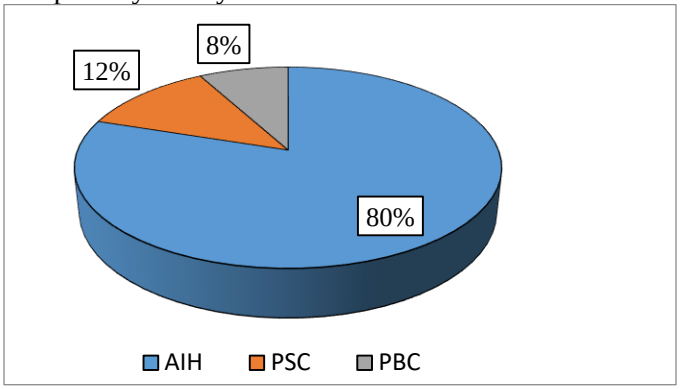

Figure (2): Final diagnosis among enrolled patients with autoimmune liver diseases

Characteristic of patients based on final diagnosis (table 4-5):

It was found that all patients with PSC were males and 39 (97.5%) patients with AIH were males, while male/female ratio was 1:1 in case of PBC.

Fatigue and itching were frequently present in patients with PSC and PBC. Jaundice was frequently present in patients with AIH and PSC.

Patients with PSC had the highest level of alkaline phosphatase (575.87 ± 84.09 (u/l).

Table (4): Baseline characteristic of enrolled patients based on final diagnosis

	AIH (n= 40)	PSC (n= 6)	PBC (n= 4)	*P* value
Age	41.17 ± 5.81	46 ± 8.08	36.10 ± 3.13	0.16
Age group				0.93
< 20 years	2 (5%)	0	0	
20-40 years	24 (60%)	4 (66.7%)	2 (50%)	
> 40 years	14 (35%)	2 (33.3%)	2 (50%)	
Sex				**< 0.001**
Male	1 (2.5%)	6 (100%)	2 (50%)	
Female	39 (97.5%)	0	2 (50%)	
Diabetes mellitus	7 (17.5%)	1 (16.7%)	0	0.66
Hypertension	5 (12.5%)	0	1 (25%)	0.48
Smoking	2 (5%)	0	0	0.77
Disease duration (years)	2.83 ± 1.56	2.50 ± 1.97	3.50 ± 0.58	0.61
Jaundice	39 (97.5%)	6 (100%)	1 (25%)	**< 0.001**
Fatigue	32 (82.5%)	6 (100%)	4 (100%)	**0.04**
Itching	5 (12.5%)	6 (100%)	4 (100%)	**< 0.001**
Fever	6 (15%)	0	2 (50%)	0.10
Abdominal pain	16 (40%)	2 (33.3%)	2 (50%)	0.87
Hematemesis& melena	4 (10%)	0	0	0.58
Hepatic encephalopathy	7 (17.5%)	1 (16.7%)	0	0.66

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. AIH: autoimmune hepatitis; PSC: primary sclerosing cholangitis; PBC: primary biliary cirrhosis

Table (5): Laboratory and imaging data of patients based on final diagnosis

	AIH (n= 40)	PSC (n= 6)	PBC (n= 4)	*P* value
Hepatomegaly	7 (17.5%)	3 (50%)	0	0.10
Splenomegaly	25 (62.5%)	4 (66.7%)	0	**0.04**
Ascites	8 (20%)	2 (33.3%)	0	
Biliary stricture	0	6 (100%)	0	< **0.001**
Hemoglobin (mg/dl)	10.77 ± 1.44	10.71 ± 1.82	11.35 ± 1.32	0.75
Platelets (ul/10^3)	157.44 ± 9.10	189.98 ± 34.56	167.34 ± 34.45	0.14
Leucocytes (ul/10^3)	11.45 ± 2.34	10.01 ± 2.01	9.87 ± 2.01	0.81
INR	1.43 ± 0.39	1.27 ± 0.3	1.21 ± 0.23	0.17
Bilirubin (mmol/l)	183.98 ± 8.34	162.83 ± 8.11	177.11 ± 34.91	0.92
Direct bilirubin (mmol/l)	100.99 ± 23.45	108.25 ± 5.99	112.45 ± 26.87	0.97
Albumin (mg/dl)	30.27 ± 6.71	32.33 ± 3.20	35 ± 2.31	0.21
Aspartate transaminase (U/L)	226.45 ± 45.98	210 ± 34.01	222.48 ± 43.91	0.58
Alanine transaminase (U/L)	218.97 ± 22.34	200 ± 21.98	210.88 ± 32.01	0.62
Alkaline phosphatase (U/L)	218.72 ± 33.45	575.87 ± 84.09	237.34 ± 8.40	**0.03**
Immunoglobulin (g/dl)	1.86 ± 0.4	1.66 ± 0.1	1.72 ± 0.1	0.47
Positive ANA	33 (82.5%)	2 (33.3%)	1 (25%)	< **0.001**
Positive ASMA	19 (50%)	3 (50%)	2 (50%)	0.99
Positive AMA	0	0	4 (100%)	< **0.001**
Positive anti-LKMA	2 (2.5%)	0	0	0.34

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. AIH: autoimmune hepatitis; PSC: primary sclerosing cholangitis; PBC: primary biliary cirrhosis; INR: international randomized ratio; ANA: antinuclear antibody; ASMA: anti-smooth antibody; AMA: anti mitochondrial antibody; LKMA: liver kidney microsomal antibody

Treatment and outcome among patients with autoimmune liver diseases (table 6):

It was found that 40 (80%) patients received steroid therapy while 12 (24%) patients received immunosuppressive agents in form of Imuran.

Two patients with AIH developed decompensated liver cirrhosis and underwent liver transplantation.

Majority (94%) of patients were alive while only three patients were deteriorated and died secondary to massive attack of hematemesis; two patients with AIH and another patient had PSC.

Table (6): Treatment and outcome among patients with autoimmune liver diseases

	N= 50
Treatment	
Steroid	40 (80%)
Immunosuppressive agent	12 (24%)
UDCA	15 (30%)
Liver transplantation	2 (4%)
Outcome	
Alive	47 (94%)
Died	3 (6%)

Data expressed as frequency (percentage). UDCA: ursodexoycholic acid

DISCUSSION

The frequency of AILD in the current study was 2.9% with mean age of 37.5 years and female predominance (80%). Out of those patients with AILD; AIH was present in 40 (80%) patients, 6 (12%) patients had PSC while 4 (8%) patients had PBC. A previous study, found that 5.7% had AILD and up to 74% of them were females. The authors stated that those 5.7% patients were subdivided as following; AIH (4.5%), PBC (0.56%), PSC (0.28%) and overlap syndrome (0.34%) [8]. Western countries had higher frequency of AILD was 11–23% [9]. This discrepancy in frequency of ALD may be attributed to genetic bases but the complete etiology wasn't known.

Generally, frequency of AILD was fairly uncommon. Over 7- years duration only 39 and 50 cases were diagnosed to have AIH in two previous studies [10, 11]. Another two studies reported that overlap syndrome present in10 and 27 cases over a 2-year duration [12, 13].

Here, PSC present only in males while up to 98% of AIH were males and 1:1 ratio as regards gender occurred in PBC. Previous studies found that AILD had male: female ratio was 1/3:8 with peak age between 4-65 years and may be associated with autoimmune condition as diabetes mellitus [10-13]. In line with the current, PBC is a rare disease in all populations as reported by previous studies [14, 15]. Till now, there is paucity in the studies about clinical pattern and course of AILD and in particularly overlap syndrome. Previous study found that 54% of patients with AIH/PBC overlap developed portal hypertension while this sequel occurred in only 28% with AIH with need to liver transplantation occurred in 38 vs. 19% respectively [16]. Similar to our study, two studies found that PSC was relatively low where it was found in 18 patients over 10-years duration [17] and in 6 patients over 4-years duration [18]. Few case series have described overlap syndrome, more specifically PBC/AIH overlap syndrome. None of the patients in the current study had overlap syndrome [18].

The current study's main limitations included: 1) a small patient sample size, 2) a retrospective design, and 3) we are unable to perform survival among those patients due to missing data on survival duration. However, to the best of our knowledge, this is the first study that looked at the pattern and distribution of AILD in our area.

CONCLUSION

ALDs are frequently diagnosed too late. To detect them early, they should be suspected in all hepatic patients, particularly middle-aged women who do not drink and do not have a viral etiology. The presence of known autoimmune diseases should alert clinicians to the presence of AILD in these patients.

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Conflict of Interest: No

Acknowledgments: No

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