European Journal of Internal Medicine 85 (2021) 86–91

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Alcoholic liver disease and autoimmune hepatitis: Sometimes a closer look under the surface is needed

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ARTICLE INFO

Keywords:
Alcoholic liver disease
Autoimmune hepatitis
Liver autoimmune serology
Alcohol-use disorder
Cirrhosis
Outcome

ABSTRACT

Aims: Differential diagnosis of autoimmune hepatitis (AIH) incorporates various liver diseases, including alcoholic liver disease (ALD). We report on clinical, laboratory and outcome characteristics of AIH patients who were initially referred as ALD based on increased alcohol consumption (AIH/ALD).

Methods: From 2000-2019, we retrospectively identified 12 AIH/ALD patients [9 males, age: 61 (30-73) years] in our prospective data base of 317 AIH patients.

Results: AIH diagnosis was based on aminotransferases elevation in 10 patients, high IgG in 8, compatible autoantibody profile in all and typical/compatible histology in all 9 with available biopsy. There were no significant differences of baseline demographics, presentation, cirrhosis at diagnosis, response to treatment and simplified score compared to 45 age- and sex-matched AIH patients without alcohol consumption and 44 age- and sex-matched ALD patients. However, the AIH/ALD cohort was characterized by more frequent progression to cirrhosis, higher liver-related deaths and overall mortality compared to AIH, though similar to the ALD group. AST/ALT ratio>1 seems to bear a good positive (0.84) and negative predictive value (0.88) for ALD and AIH diagnosis, respectively, but cannot help in discriminating the AIH/ALD variant.

Conclusions: AIH should not be forgotten in patients with alcohol use when clinical and laboratory features hint towards the diagnosis of AIH/ALD variant as this group seems to have worse outcome compared to those with AIH alone suggesting the need for closer follow-up and surveillance. Reliable autoantibody testing and cautious interpretation of liver histology appear mandatory for AIH diagnosis in these difficult to diagnose cases.

1. Introduction

Autoimmune hepatitis (AIH) is a heterogeneous disease of unknown etiology, its basic characteristics being circulating autoantibodies, hypergammaglobulinaemia and interface hepatitis [1–4]. AIH exhibits a wide diversity mainly in terms of clinical manifestations ranging from acute severe hepatitis and/or fulminant hepatitis to insidious disease presenting either with non-specific symptoms or being entirely asymptomatic. Although female sex predominates, it is now recognized that AIH can affect both sexes of all age and ethnic groups [1–4]. The wide spectrum of clinical characteristics in conjunction with absence of disease-specific laboratory and histologic features, renders its diagnosis often difficult and challenging, as it could concur with other autoimmune diseases [5–9] and a large spectrum of acute and chronic hepatopathies such as viral hepatitis, non-alcoholic fatty liver disease (NAFLD), autoimmune cholestatic syndromes and drug-induced liver injury [1,3,10–16]. In this context, data on coincidence of AIH with alcoholic liver disease (ALD) or an alternative AIH diagnosis instead of

Abbreviations: AIH, autoimmune hepatitis; NAFLD, non-alcoholic fatty liver disease; ALD, alcoholic liver disease; AUD, alcohol use disorder; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; LKM-1, liver/kidney microsomal type 1; LC1, liver cytosol type 1; SLA/LP, soluble liver antigens/liver pancreas; MMF, mycophenolate mofetil; AZA, azathioprine; EASL, European Association for the Study of the Liver; HASL, Hellenic Association for the Study of the Liver; CR, complete response; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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https://doi.org/10.1016/j.ejim.2020.12.024
Received 25 August 2020; Received in revised form 25 December 2020; Accepted 27 December 2020
Available online 12 January 2021

Table 1
Baseline characteristics of AIH/ALD, AIH and ALD patients

	AIH/ ALD patients n=12	AIH patients n=45	ALD patients n=44	AIH/ ALD vs. AIH p value	AIH/ ALD vs. ALD p value	AIH vs. ALD p value
Sex (male/female)	9/3	26/19	22/12	ns	ns	ns
Age at diagnosis (years)	61 (30-73)	45 (18-79)	55 (31-71)	ns	ns	ns
Duration to diagnosis (months)	8.5 (1-144)	7 (0-192)	5 (0-60)	ns	ns	ns
Symptoms at diagnosis (yes/no)	7 /5	24 /21	20 /24	ns	ns	ns
Disease presentation (acute/insidious)*	4 /8	18 /27	16 /28	ns	ns	ns
Cirrhosis at diagnosis (yes/no)**	5 /7	7 /38	14 /30	ns	ns	ns
Concurrence of other autoimmune diseases (yes/no)***	3 /9	16/29	0/44	ns	0.008	<0.001
Family history of autoimmune disease (yes/no)	1/11	4/41	0/44	ns	ns	ns
Alcohol (units/day)	3.5 (3-30)	0.1 (0-2)	7.5 (5-60)	<0.001	0.02	<0.001
Duration of alcohol abuse (years)	30 (10-45)	-	25 (4-50)	-	ns	-
BMI (kg/m^2)	23 (18-29)	26 (23-32)	28 (19-40)	ns	ns	ns
Detection of autoantibodies	n=12	n=45	n=10			
• ANA	7 (58%)	34 (76%)	6 (60%)	ns		
• SMA	12 (100%)	42 (93%)	6 (60%)	ns		
• Anti-SLA/LP	3 (25%)	2 (4%)	0 (0%)	ns		
• Anti-LKM• Anti-LC1• Anti-SLA/LP, anti-LKM, anti-LC1	2 (17%)	5 (11%)	0 (0%)	ns		
• Anti-LC1	1 (8%)	0 (0%)	0 (0%)	ns		
• Anti-SLA/LP, anti-LKM, anti-LC1	6 (50%)	7 (16%)	0 (0%)	0.02	0.01	<0.001
ALT (IU/L; ULN=40)	87 (7-1073)	320 (15-2871)	44 (13-180)	0.05	0.04	<0.001
AST (IU/L; ULN=40)	105 (17-1155)	189 (10-1508)	68 (22-354)	ns	ns	0.001
AST/ALT ratio >1 (yes/no)	7/5	8/37	38/6	0.005	0.05	<0.001
AST/ALT ratio	1.1 (0.7-4)	0.7 (0.3-2)	1.6 (0.4-6.4)	<0.001	0.04	<0.001
γ GT (IU/L; ULN=38)	181 (61-473)	116 (8-566)	237 (40-1481)	ns	ns	<0.001
ALP (IU/L, ULN=104)	96 (35-383)	112 (29-201)	85 (33-269)	ns	ns	ns
Bilirubin total (mg/dL, ULN=1.1)	6 (4-19)	2.5 (4-26)	1.4 (0.4-14)	ns	ns	ns
IgG (>ULN)#	8 (67%)	26 (58%)	7 (29%)	ns	ns	0.02
Liver biopsy	n=9	n=40	n=4			
• Grading (mild or moderate/severe or cirrhosis)	2/7	14/26	4/0	ns	na	na
• Staging (mild or moderate/severe or cirrhosis	6/3	29/10	3/1	ns	na	na
Simplified score	6.5 (5-9)	6 (4-12)	na	ns	na	na

ns, not statistically significant. na, not applicable. Abbreviations are same as in the text. ALP, alkaline phosphatase; ULN, upper limit of normal; BMI, body mass index. Data are expressed as median (range) where appropriate.

* As we have previously described [6,11,25,26], the mode of disease presentation was defined as (a) insidious, when either liver biochemistry was increased in the absence of symptoms or there were non-specific symptoms sometimes dating back years (i.e. fatigue, anorexia, arthralgia, right upper quadrant pain, weight loss, pruritus, polyarthralgia affecting the small joints without arthritis etc.) and (b) as acute, when icteric hepatitis as designated by a recent increase of aminotrasferases above 10 times the upper limit of normal in conjunction with jaundice was present [26,27].

** For cases without available biopsy, the diagnosis of cirrhosis was based on either ultrasonography (nodules in liver, spleen >12 cm, portal vein >16 mm), or elastography (liver stiffness >12 kPa), or endoscopic findings of cirrhosis (varices, portal gastropathy), and/or clinical findings of decompensation (ascites, variceal bleeding, encephalopathy) [34–36].

*** Concurrence of other autoimmune diseases: AIH/ALD patients, 1 with Hashimoto's thyroiditis, 1 with idiopathic thrombocytopenic purpura, and 1 with chronic inflammatory demyelinating polyneuropathy; AIH patients, 5 with Hashimoto's thyroiditis, 3 with celiac disease, 2 with Biermer's anemia, 2 with systemic lupus erythematosous, 2 with rheumatoid arthritis, 1 with ulcerative colitis and 1 with retroperinoneal fibrosis.

IgG was tested in 24 ALD patients at the initial evaluation.

ALD is missing.

ALD is inextricably linked to alcohol-use disorder (AUD) and represents one of the leading causes of cirrhosis and liver-related mortality worldwide. ALD encompasses a wide clinical spectrum of disorders, ranging from asymptomatic hepatic steatosis, to alcoholic steatohepatitis and cirrhosis, while acute-on chronic liver failure and alcoholic hepatitis represent distinct entities [17–19].

The diagnosis of ALD relies mainly on documentation of alcohol consumption, while exclusion of other causes of liver disease is also mandatory. Existing data have shown liver disease of various etiologies to coexist with ALD [20,21]. Considering overlapping characteristics often shared between AIH and ALD, it is often mandatory to assess individual patients with an apparent "ALD phenotype" for AIH as hinted by individual clinical or laboratory characteristics that largely remain overlooked.

Accordingly, we present 12 patients that were initially referred to our department as possible ALD, though during evaluation were diagnosed with AIH, as similar data on AIH/ALD variant is scarce.

2. Patients and Methods

Between 2000 and 2019, we identified in our prospective database of a total number of 317 AIH patients, 12 patients [9 males; median age at presentation: 61 years (range: 30-73)] that were initially referred to our department as ALD but after further assessment an additional or alternative AIH diagnosis was established based on internationally accepted criteria (AIH/ALD patients) [2–4,22]. ALD diagnosis was considered in all patients based on increased alcohol intake, as evidenced by more than two and three drinks daily for males and females respectively, each containing 10 g of alcohol [18,23]. In addition, we report on the total duration of alcohol consumption preceding their first evaluation in our department, as recent compared to previous alcohol consumption has been linked to increased risk of alcoholic cirrhosis [24].

Medical files of these patients were reviewed retrospectively and data on demographics, clinical and laboratory parameters at initial evaluation as well as outcome measures were recorded. In addition, data on treatment schedule and treatment response were collected. Patients were on 3-6 months of follow-up according to the individual patient condition and treatment requirements.

We have selected two groups of patients to serve as disease controls. The first consisted of 45 randomly assigned age and sex-matched patients with well-established AIH [26 males, 1:3.8 ratio to AIH/ALD patients; median age at presentation: 45 (18-79) years] (AIH patients) and the second group included 44 randomly assigned age and sex-matched patients with ALD [22 males, 1:3.7 ratio to AIH/ALD patients; median age at presentation: 52 (31-71) years] (ALD patients).

A liver biopsy was performed when feasible and assessed by the Knodell histological activity index score [25]. In accordance to our previous work [26–28], patients were divided into those having minimal/mild (score: 0-8) and moderate/severe (score: 9-18) necroinflammatory activity. Concerning fibrosis assessment, patients were categorized as having mild/moderate fibrosis (score: 0-2) and severe fibrosis/cirrhosis (score: 3-4). As we have reported previously, the diagnosis of cirrhosis was based on standard clinical, laboratory and/or histological data (Table 1) [29–31].

Determination of autoantibodies was performed in all patients as described previously [2,3,32,33]. Briefly, indirect immunofluorescence on 5-μm fresh frozen sections on in-house rodent kidney, liver, stomach tissue substrates, was utilized for testing of antinuclear (ANA), smooth muscle antibodies (SMA), liver/kidney microsomal type 1 (anti-LKM-1) and liver cytosol type 1 (anti-LC1) antibodies. Immunoblotting using rat liver microsomal or cytosolic extracts was also applied for the evaluation of anti-LKM-1, anti-LC1 and antibodies against soluble liver antigens/liver pancreas (anti-SLA/LP) [32–35]. These autoantibodies were also assessed by commercially available ELISAs (INOVA, Diagnostics Inc., San Diego, CA, USA for anti-LKM1 and anti-SLA/LP and EUROIMMUN Medizinische Labordiagnostica AG, Lübek, Germany for anti-LC1).

All patients were negative for hepatitis A, B, C and E, while also metabolic and other toxic components such as, Wilson's disease and drug induced liver injury were appropriately excluded. The descriptive criteria of the International AIH Group as well as the simplified score were applied to facilitate the clinical diagnosis of AIH [22,36].

Treatment either with prednisolone plus mycophenolate mofetil (MMF) or prednisolone plus azathioprine (AZA) was scheduled according to the Hellenic Association for the Study of Liver Diseases (HASL) and European Association for the Study of Liver Diseases (EASL) guidelines as well as according to our previous work [2–4,26–28]. In brief, patients with AIH/ALD or AIH alone were started on prednisolone (0.5-1 mg/kg/day) that was gradually tapered according to the biochemical and clinical response up to withdrawal [2,3]. In accordance with existing data, MMF (1.5-2 g/day) or AZA (1-2 mg/kg/day) was maintained for at least 2 years after complete response (CR) was achieved. Treatment endpoints were defined according to published clinical practice guidelines [2–4].

All patients consented to participate in this study. The ethical committee of the General University Hospital of Larissa approved the protocol which conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.1. Statistics

Data are presented as mean±standard deviation or median (range) as appropriate. Data were analyzed by Mann-Whitney U-test, t-test, x^2 (two-by-two with Yate's correction), Fisher's exact test, Kruskal-Wallis analysis of variance, where applicable. Two-sided $P < .05$ were considered statistically significant. The 17th edition of the SPSS statistical program was used for analysis.

3. Results

3.1. Characteristics of AIH/ALD patients at initial evaluation

The AIH/ALD patients' characteristics are shown in Table 1 and supplementary Table 1. The majority of AIH/ALD patients were men (9/12; 75%), 7 (58%) of them exhibiting symptoms at diagnosis, while the presentation was insidious in 8 (67%; Table 1). Comparison between AIH/ALD, AIH and ALD patients did not reveal any significant differences in terms of baseline demographic and clinical characteristics except for higher frequency of other concurrent autoimmune diseases in AIH/ALD and AIH compared to ALD patients ($p \leq 0.008$ for both comparisons) and lower alcohol consumption in AIH compared to AIH/ALD and ALD patients ($p<0.001$ for both; Table 1).

Moreover, AIH/ALD patients were characterized by significant higher frequency of liver specific autoantibodies compared to AIH ($p=0.02$) and ALD ($p=0.01$) patients. Similarly, AIH patients had more frequently liver specific autoantibodies compared to ALD patients ($p<0.001$; Table 1).

AIH/ALD and ALD patients had significantly lower alanine aminotransferase (ALT) levels compared to AIH ($p=0.05$ and $p<0.001$, respectively); being also significantly lower in ALD vs. AIH/ALD ($p=0.04$; Table 1).

There were significant differences in the frequency of aspartate aminotransferase (AST)/ALT ratio>1 among all 3 groups, ALD patients having the highest frequency (86%) compared to AIH/ALD (58%) and AIH (18%) patients ($p \leq 0.05$ for comparisons in the 3 groups; Table 1). AST/ALT ratio>1 had a negative predictive value of 0.88 for AIH diagnosis and a positive predictive value of 0.84 for ALD diagnosis. On the contrary, AST/ALT ratio>1 displayed low positive and negative predictive values during work up of patients with AIH/ALD variant (0.47 and 0.45, respectively).

AST/ALT ratio>1 in AIH/ALD patients was associated with the presence of cirrhosis in 3 patients and in the majority of non-cirrhotic patients (75%) with excessive alcohol consumption (>10 units/day). Of note, an AST/ALT ratio>1 was associated with the presence of cirrhosis in 63% of the AIH group.

AIH patients had significantly more frequent IgG levels above the

Table 2
Treatment response and outcome data of AIH/ALD, AIH and ALD patients

	AIH/ALD patients n=12	AIH patients n=45	ALD patients n=44	AIH/ ALD vs. AIH p value	AIH/ ALD vs. ALD p value	AIH vs. ALD p value
Disease duration (months)	31.5 (5-200)	93 (1-303)	65 (14-284)	ns	ns	0.03
Total follow up (months)	24 (5-187)	57 (1-210)	57 (1-210)	ns	ns	ns
Age at last follow up (years)	63 (37-80)	53 (31-84)	62.5 (34-78)	ns	ns	ns
Immunosuppressive treatment (yes/no)	9/3	43/2	na	ns	na	na
Duration of immunosuppression (months)	30 (4-119)	61 (5-222)	na	0.02	na	na
Outcome						
Development of cirrhosis (yes/no)	2/5	0/38	3/27	0.02	ns	0.03
Decompensation of cirrhosis (yes/no)	2/5	0/7	4/13	ns	ns	ns
Development of hepatocellular carcinoma (yes/no)	1/11	0/45	2/42	ns	ns	ns
Liver-related death (yes/no)	2/10	0/45	4/40	0.04	ns	0.06
Response to treatment overall	n=9	n=43				
• Complete response	5 (56%)	2 (22%)				
• Partial response	27 (63%)	1 (2%)	na	ns	na	na
• Response with relapses during treatment	2 (22%)	15 (35%)				

ns, not statistically significant. na, not applicable. Abbreviations are same as in the text.

upper limit of normal compared to ALD patients (p=0.02; Table 1), while there were no differences between AIH and AIH/ALD patients. Nine AIH/ALD patients underwent liver biopsy, including 7 patients with moderate or severe necroinflammatory activity and 3 with severe fibrosis. A liver biopsy was not carried out at initial evaluation in 3 patients because of coagulation disturbances, including 1 patient with severe thrombocytopenia due to idiopathic thrombocytopenic purpura, that rendered the procedure unsafe. However, all these 3 AIH/ALD and 5/45 AIH patients without available liver biopsy fulfilled the rest criteria for a definite AIH diagnosis like positive liver autoimmune serology, increased IgG, exclusion of viral hepatitis and favorable response to immunosuppression.

All patients had histological features compatible or typical with AIH, including interface hepatitis with lymphoplasmocytic infiltrate rich in plasma cells, hepatocyte rosetting and emperipolesis. None of patients had simple steatosis while only 2 of 9 (22%) had co-existing features compatible with ALD (i.e. steatohepatitis with presence of Mallory bodies). No differences were noted in median simplified scores between AIH/ALD and AIH groups (Table 1) as well as in antibody titers between AIH/ALD and AIH patients (data not shown).

3.2. Treatment

Nine patients (75%) received immunosuppressive treatment, while according to the guidelines [2,3], the remaining 3 were excluded either because of minimal necroinflammatory activity on liver biopsy (2 patients) or decompensated cirrhosis (1 patient). Seven (78%) patients received combination regimen with prednisolone and MMF, as part of a protocol run by our Department [26–28], while 2 (22%) received conventional immunosuppression (prednisolone plus AZA) as they did not consent to participate in the above-mentioned protocol.

Forty-three AIH patients were treated [31 (72%) with prednisolone and MMF, 11 (26%) with conventional immunosuppression and 1 (2%) with prednisolone monotherapy]. Nine of 11 patients that received initially prednisolone and AZA combination were converted to MMF either due to adverse effects or due to failure to achieve CR.

There were no significant differences regarding the on treatment CR, partial response or relapses (Table 2). The point prevalence of CR at last follow-up was 78% for AIH/ALD and 98% for AIH patients.

There was no significant difference between AIH/ALD and AIH groups regarding the duration of therapy till the time of first CR [4(1-6) vs. 4(1-36) months; p=0.6] as well as on the percentage of patients on dual treatment that stopped prednisolone during follow-up and the percentage of patients that relapsed after steroid withdrawal during follow-up (data not shown).

Outcome During follow-up, 2, 0 and 3 non-cirrhotic patients from the AIH/ALD, AIH and ALD groups, respectively, developed cirrhosis (p=0.02 and p=0.03; Table 2).

In total, 2 (17%) AIH/ALD, 4 (9%) ALD patients and none of the AIH patients died due to liver-related death during follow-up (p=0.04 for AIH/ALD vs. AIH and p=0.06 for AIH vs. ALD; Table 2).

4. Discussion

We herein report on 12 patients that were originally referred to our department with a presumed ALD diagnosis solely based on increased daily alcohol consumption (>5 units in the majority) and were subsequently diagnosed with AIH after thorough consideration of clinical and laboratory features, that are considered “red flags” for AIH. Our purpose was to delineate the importance of recognizing individual parameters that could easily help physicians to distinguish between AIH and ALD. This is of outmost importance considering existing data demonstrating increased adverse events and liver-related mortality if both diseases remain undiagnosed and untreated [2,3,17–19,37]. As we have reported recently, the same problem exists concerning the differentiation between AIH and NAFLD [10] underlying the difficulties which may raise in diagnosing AIH in patients with concurrent other co-morbidities.

ALD accounts for a considerable part of cirrhosis burden globally, while liver-related mortality due to alcohol is reportedly increasing [38, 39]. Importantly, alcohol is also a significant co-factor for the progression of liver diseases of various etiologies, as clearly highlighted in the case of viral hepatitis and iron overload disorders [20,21].

Clinical and laboratory findings of ALD patients vary greatly, display no specific features and diagnosis relies mainly on relevant history of amount and type of alcohol consumption [18,19,24]. In this regard, interpreting clinical and laboratory data as ALD-specific having as only criterion the increased consumption, could easily lead to wrong clinical judgement and diagnosis and subsequent to inappropriate therapeutic choices.

ALD requires a multidisciplinary approach depending on the disease stage, while integrating management for AUD is also mandatory [18, 19]. In the case of AIH, prompt and timely diagnosis of AIH seems mandatory in an attempt to achieve a favorable outcome [1–4,40].

Existing literature indicates that both AIH and ALD cannot be distinguished from each other or from other forms of liver disease based on presence of symptoms or mode of presentation [2,4,18, 19]. Importantly, there were no significant differences in terms of the mode of disease presentation, symptoms at presentation, presence of concurrent autoimmune diseases between the AIH/ALD and AIH group. It is worth mentioning, that the majority of AIH/ALD patients were men in their 6th decade of life, which is not the norm in the typical AIH population.

In our case, careful evaluation towards concurrence of AIH in patients with underlying ALD were the significant increase in transaminase levels above those considered compatible with ALD (AST and/or ALT>300), preponderance of ALT over AST in a proportion of patients and additionally increased IgG in similar frequency to the AIH patients. Still, some differences between AIH/ALD and AIH patients could indicate synergistic effect of both causes in eliciting liver injury. Regarding this, ALT levels were lower in AIH/ALD compared to AIH patients, which is in accordance with existing knowledge showing ALT levels to be lower to AST in ALD. In this context, a significant larger number of AIH/ALD patients had AST/ALT ratio>1 compared to AIH, which was mainly associated with increased alcohol consumption in the former and presence of cirrhosis in the latter group. Still, AST/ALT ratio>1 exhibited good negative and positive predictive values towards diagnosis of AIH and ALD, respectively. However, AST/ALT ratio>1 seems not very helpful to discriminate the AIH/ALD variant from ALD or AIH (NPV: 45% and PPV: 47%, respectively) probably because of the low number of patients with the variant.

Autoantibody testing has a fundamental role during evaluation of suspected AIH, when complying with published guidelines [1–4,32–35]. All our AIH/ALD patients had at least one autoantibody detected at initial evaluation, while half of them were positive for anti-SLA/LP, anti-LKM-1 or anti-LC1. Except for diagnostic purposes, testing for liver-specific autoantibodies has also prognostic value, as has been shown for anti-SLA/LP that can serve as a marker of lifelong immunosuppression [41,42].

Although we have no available data on HLA typing or other genetic factors, we cannot exclude the probability of alcohol having acted as a trigger of autoimmune responses in genetically predisposed individuals [43]. Early studies have reported on the presence of low-titers autoantibodies mostly related with advanced ALD, suggesting they could represent immune responses having resulted from alcohol-induced liver damage [44]. Lately, experimental data have provided evidence to support the pivotal role of alcohol metabolism products, including acetaldehyde, malondialdehyde and alcohol dehydrogenase, in inducing autoantibodies [45].

AIH diagnosis was histologically validated in three quarter of AIH/ALD patients having undergone a liver biopsy, displaying either compatible or typical for AIH in all. While histological evaluation is a prerequisite for AIH diagnosis [2–4], it is not essential for ALD, unless a definite diagnosis is warranted or exclusion of other liver diseases is

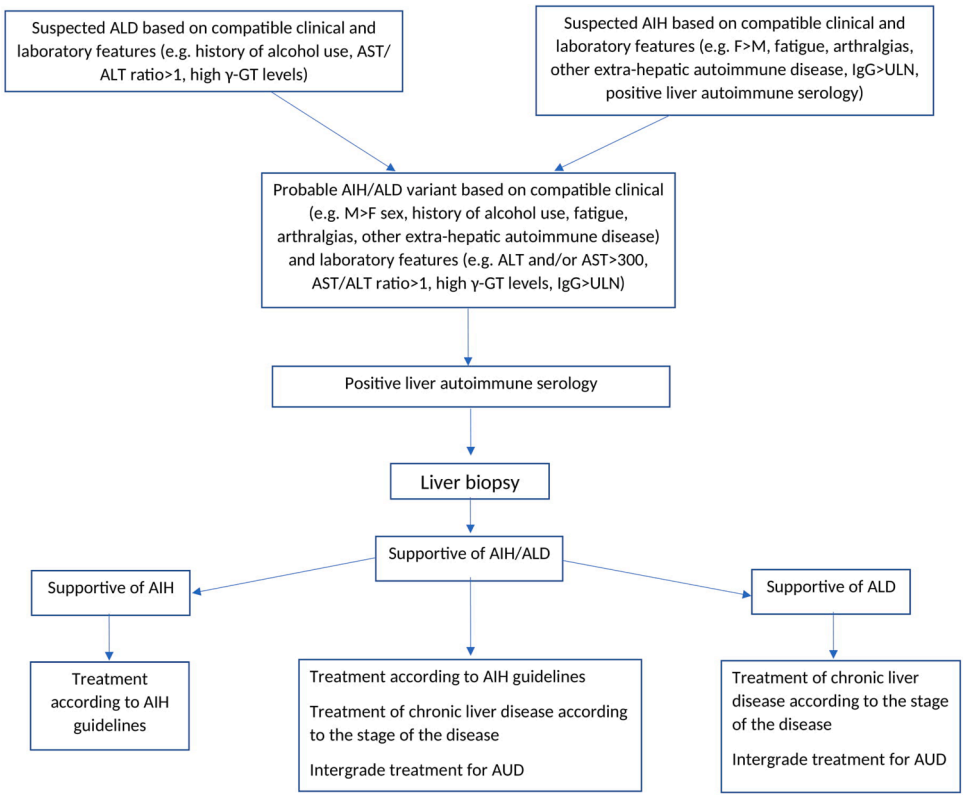

Fig. 1. Proposed diagnostic and treatment algorithm for AIH/ALD patients. AIH, autoimmune hepatitis; ALD, alcoholic liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, gamma-glutamyl transpeptidase; F, female; M, male; IgG, immunoglobulin G, ULN, upper limit of normal; AUD, alcohol use disorder.

mandated [18,19]. Less than a quarter of biopsied patients had also features of ALD, even though all patients were consuming actively alcohol. This is not surprising since a dissociation between clinical and histological diagnosis of ALD has been long recognized [18,19].

The simplified score has merely facilitated AIH diagnosis in every day clinical practice, though should not be considered a panacea given several limitations especially in acute hepatitis and children cases, as well as in those with concurrence of other liver diseases (i.e. AIH and NAFLD, AIH and viral hepatitides and AIH and drug- or toxin-induced liver disease) [1–5,10,11,33,46].

Our AIH/ALD cohort was characterized by more frequent progression to cirrhosis, higher liver-related deaths and overall mortality compared to the AIH patients. However, we cannot exclude the possibility that some of these patients were continuing to consume alcohol, either regular or intermittently, which could have had contributed to faster progression of liver disease, as also shown in ALD patients.

In conclusion, this report underscores the importance for the primary care physicians and internists in assessing patients reporting alcohol abuse for the presence of AIH if individual clinical and laboratory features are suggestive such as male sex, high IgG levels, AST and/or ALT>300. Reliable liver autoimmune serology testing and cautious interpretation of histology seem indispensable tools for an additional AIH diagnosis. In this respect, we propose a diagnostic and therapeutic algorithm for AIH/ALD patients (Fig. 1). From the clinical point of view, it is imperative to be able to recognize patients with AIH/ALD variant as this group seems to have worse outcome compared to those with AIH alone suggesting also the need for closer follow-up and surveillance of these patients. However, long-term multicenter studies are needed in order to draw definite general conclusions on the prevalence and clinical consequences of patients with AIH/ALD variant.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2020.12.024.

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