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REVIEW

Auto immune hepatitis

Nicole MF van Gerven, Ynto S de Boer, Chris JJ Mulder, Carin MJ van Nieuwkerk, Gerd Bouma

Nicole MF van Gerven, Ynto S de Boer, Chris JJ Mulder, Carin MJ van Nieuwkerk, Gerd Bouma, Department of Gastroenterology and Hepatology, Vu University Medical Centre, 1081 HV, Amsterdam, The Netherlands

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Correspondence to: Chris JJ Mulder, Professor, Department of Gastroenterology and Hepatology, Vu University Medical Centre, De Boelelaan 1118, 1081 HV Amsterdam, The Netherlands. cjmulder@vumc.nl
Telephone: +31-20-4440613
Fax: +31-20-4449406

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Abstract

To provide an update of the latest trends in epidemiology, clinical course, diagnostics, complications and treatment of auto immune hepatitis (AIH). A search of the MEDLINE database was performed using the search terms: "auto immune hepatitis", "clinical presentation", "symptoms", "signs", "diagnosis", "auto antibodies", "laboratory values", "serology", "histopathology", "histology", "genetics", "*HLA* genes", "*non-HLA* genes", "environment", "epidemiology", "prevalence", "incidence", "demographics", "complications", "HCC", "PBC", "PSC", "corticosteroid", "therapy", "treatment", "alternative treatment". English-language full-text articles and abstracts were considered. Articles included reviews, meta-analysis, prospective retrospective studies. No publication date restrictions were applied. AIH is an immune meditated progressive inflammatory liver disease that predominantly affects middle-aged females but may affect people of all ages. The clinical spectrum of AIH is wide, ranging from absent or mild symptoms to fulminant hepatic failure. The aetiology of AIH is still unknown, but is believed to occur as the consequence of an aberrant immune response towards an un-known trigger in a genetically susceptible host. In the absence of a gold standard, diagnosis is based on the combination of clinical, biochemical and histopathological criteria. Immunosuppressive treatment has been the cornerstone of treatment since the earliest description of the disease in 1950 by Waldenström. Such treatment is often successful at inducing remission and generally leads to normal life expectancy. Nevertheless, there remain significant areas of unmet aetiological a clinical needs including fundamental insight in disease pathogenesis, optimal therapy, duration of treatment and treatment alternatives in those patients unresponsive to standard treatment regimens.

Key words: Auto immune hepatitis; Diagnosis; Liver; Epidemiology; Treatment

Core tip: Autoimmune hepatitis (AIH) is a chronic inflammatory liver disorder of unknown aetiology, which can lead to hepatic failure and premature

death when untreated. In AIH there is no existence of a pathognomonic feature and therefore the diagnosis rests on a combination of immunological, biochemical, and histological features together with exclusion of other liver diseases. Due to large heterogeneity of the disease, AIH might be unrecognised. Immunosuppressive treatment has been the cornerstone of treatment. Such treatment is often successful at inducing remission. For most patients life long treatment is indicated. In patients in whom all treatments fail, liver transplantation remains a final option.

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INTRODUCTION

The first to describe a chronic form of hepatitis in young women was Jan Waldenström in 1950[1]. Later, the disease was associated with other autoimmune diseases and was termed "lupoid hepatitis" because of the presence of antinuclear antibodies and lupus erythematosus cells[2]. These observations led to the idea that the foundation of this disease was a loss of immunological tolerance. The term Auto Immune Hepatitis (AIH) in its current meaning was introduced by Mackay and colleagues in 1965 when the concept of autoimmunity was acknowledged at an international meeting[3].

AIH is now recognized as a relatively rare chronic inflammatory liver disease predominantly affecting females in which a loss of tolerance against hepatic tissue is assumed. Based on the type of serum auto-antibodies, AIH can be subdivided into two types: type 1 AIH, identifiable by antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA), and type 2 AIH, predominantly found in children and defined by antibodies against liver kidney microsomes type 1 (anti-LKM-1) or for anti-liver cytosol type 1 antibodies[4,5].

EPIDEMIOLOGY

There are few studies that have investigated the epidemiology of AIH. The majority of these studies are hampered by the fact that no predefined criteria for disease diagnosis were applied. In some older studies there has been admixture of patients with chronic hepatitis C and finally some of the studies may have been subject to tertiary referral bias (Table 1).

Nevertheless, incidence data are more or less comparable in Western Europe, ranging from 0.8 to 3 per 100000 with a prevalence ranging from 11 to 24 per 100000[5-9]. In Asia AIH seems to be less frequent, with incidence numbers ranging between 0.08 and 0.15 in Japan[10].

Substantially higher prevalence data of 42.9 cases per 100000 were found in a well defined native Alaskan population, although it should be noted that this study involved a small catchment area and a very limited number of patients[11]. Based on the available studies it is estimated that 11%-20% of all cases of chronic hepatitis in Western countries is caused by AIH[12]. The prevalence of AIH is still gradually increasing. Whether or not this reflects a true rise in incidence, as seen in other immune-mediated diseases like Crohn's disease, increased awareness of the disease or different diagnostic criteria is unknown.

Women are affected more frequently than men with a sex ratio of around 4:1[8]. 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[4,13].

PATHOGENESIS

The etiology of AIH remains unknown and fundamental questions regarding disease pathogenesis remain to be resolved. It is generally believed that AIH occurs in a genetically susceptible host as the consequence of an exaggerated immune reaction towards hepatic tissue[14]. Such a response can occur when effector lymphocyte responses are abundant and inappropriate leading to tissue damage, or, alternatively, when there is a numerical and/or functional defect in regulatory T cells (Treg) controlling such responses. This defect is more obvious at disease presentation than during treatment induced remission, where a partial recovery is observed.

Whilst abundant pro-inflammatory responses have been identified in most, if not all immune-mediated diseases, it has been very difficult to gain evidence for a primary defect in regulatory T cells in the majority of these diseases. Tregs isolated from children and adults with AIH were profoundly dysfunctional, suggesting that an underlying Treg deficiency plays a permissive role in the pathogenesis of AIH[15-17].

More recent studies omitted to find either functional or numerical Treg impairments in AIH patients and thus the question as to whether AIH is the result of defective immunoregulation warrants further investigation.

A third, not mutually exclusive mechanism may relate to molecular mimicry, which has been proposed as a mechanism by which exogenous substances may trigger an immune response against autoantigens. Such a response may spark an inflammatory reaction and the resulting hepatocellular injury may give rise to the release of other previously hidden antigens that may further fuel the inflammatory reaction. Exogenous pathogens implicated in this process include,

Table 1 Studies of incidence and prevalence of autoimmune hepatitis

Ref.	Year	Cases	Incidence/100000	Prevalence/100000
Toda *et al*[10]	1997	496	0.8	-
Whalley *et al*[125]	2007	200	3.0	-
Werner *et al*[9]	2008	473	0.85	10.7
Grønbæk *et al*[7]	2014	1721	1.68	23.9
Gerven *et al*[8]	2014	1313	1.1	18.3
Ngu *et al*[39]	2010	138	2.0	24.5
Delgado *et al*[126]	2013	100	0.67	11.0
Primo *et al*[127]	2004	13	1.37	11.61
Hurlburt *et al*[11]	2002	77	-	42.9

amongst others, the hepatitis C virus. A sequence homology between HCV polyprotein and cytochrome P4502D6 (CYP2D6) was previously reported, which was identified as anti-LKM-1 autoantibodies[18,19]. Indeed, anti-LKM-1 is seropositive in up to 10% of HCV patients. Other proposed triggers include other hepatotrophic viruses, as well as drug induced liver injury caused by antibiotics (including nitrofurantoin and minocycline), statins and anti-TNF agents[20-25].

GENETIC FACTORS

Genetic factors have long been implicated in disease pathogenesis yet systematic studies addressing the genetic epidemiology of AIH including familial occurrence, disease concordance in twins or ethnic differences in disease prevalence are lacking. Nevertheless, there are several observations that support a genetic basis for AIH. These include the association with other autoimmune diseases with a known genetic basis in up to a quarter of patients[8]. Additionally, associations with alleles of the Major Histocompatibility Complex (MHC) that encode the Human Leucocyte Antigens (HLA) were already described in the late seventies and confirmed and refined thereafter in numerous studies in different ethnic groups[26-28]. Such associations are found with most autoimmune diseases, most likely because they contribute to the specificity of immune reactions. HLA typing of patients with AIH reveals strong association with the HLA-DRB1 locus, with the haplotypes DRB1*0301 (HLA-DR3) and DRB1*0401 (HLA-DR4) as the main susceptibility factor in white Northern Europeans and North Americans[27,29-31]. Intriguingly there is evidence for substantial genetic heterogeneity in AIH with different MHC associations in different ethnic populations. Thus, in Japanese patients HLA-DRB1*0405 is the most important susceptibility allele[32,33] whereas primary associations with DRB1*0404 were found in Mexican patients[34].

The HLA alleles not only determine overall disease susceptibility but appear also to act as modifiers of the clinical phenotype. For instance, HLA-DR4 was found to be associated with female gender, less severe disease, more common autoimmune disease, and older age of onset[35-40].

Despite the fact that the MHC loci confer a 6 to 7 fold increased disease risk, these variants alone cannot explain the genetic predisposition for AIH. Genes outside the MHC have only been studied in candidate gene approaches involving limited numbers, making them prone to overestimation of significance. Most extensively studied is the cytotoxic T lymphocyte antigen-4 (*CTLA-4*) gene[41,42]. A recent study in the Netherlands involving a substantial number of patients however observed no significant differences in allele and genotype frequencies of the *CTLA-4* gene between AIH patients and controls[43].

More recently, genome-wide association studies have emerged as a powerful and unbiased approach for the identification of new genetic susceptibility loci in autoimmune diseases. Very recently this methodology was applied in a multicentre cohort of type 1 AIH patients. This study confirmed the involvement of the MHC region and identified *SH2B3* as the first genetic risk factor outside the MHC region. In addition, several other loci were identified supporting the thesis that AIH has a complex genetic basis[27].

CLINICAL FEATURES

The clinical manifestation of AIH can range from mild or severe symptoms to fulminant hepatic failure[44]. In all patients with liver disease AIH should be considered, so that that appropriate treatment can be instituted without delay. Up to 40 percent of patients presents with acute hepatitis, characterizes by right upper-quadrant abdominal pain, fatigue, jaundice and arthralgia[45]. 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[12,46-49] (Table 2).

Clinical manifestations of AIH may vary among ethnic groups. Thus, 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 when compared to Caucasian patients[44]. Higher rates of cirrhosis were found in Hispanic *vs* Caucasian patients, and a trend towards worse survival among Asians[50].

Other autoimmune diseases are common in up to

Table 2 Presentation and symptoms in auto immune hepatitis

Acute hepatitis	
Chronic hepatitis	
Hepatomegaly	
Splenomegaly	
Spider naevi	
Palmar erythema	
Non specific symptoms:	
Tiredness	
Fever	
Loss of appetite	
Upper abdominal pain	
Arthralgia	
Extrahepatic autoimmune disease (most common mentioned):	
Thyroiditis	10%-23%
Primary biliary cirrhosis	10%-20%
Diabetes	7%-9%
Primary sclerosing cholangitis	2%-8%
Rheumatoid arthritis	2%-5%
Celiac disease	1%-2%

40% of AIH patients. They included, among others thyroid disease, diabetes, inflammatory bowel disease and rheumatoid arthritis. A recent study demonstrates that celiac disease is more prevalent among AIH patients compared to the general population[51]. In addition AIH may have cholestatic features that can resemble primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) and overlap with these diseases have been described in 10%-20% and 2%-8% of cases, respectively[9,14,52-55] (Table 2). So far, there have not been uniform definitions or diagnostic criteria for the overlap of AIH with PBC or PSC. It is still under debate as to whether these overlap syndromes represent variants of the main autoimmune liver diseases or hallmarks of a separate entity[56]. The presence of features of different diseases can occur simultaneously as well as sequentially in each form of overlap syndromes. AIH and PBC are the most frequently described autoimmune liver diseases. The pattern of abnormalities in laboratory tests can help determine the origin of the disease. In AIH a hepatic pattern is found, and a primarily cholestatic pattern in PBC; in addition, elevation of IgG is characteristic of AIH, an increase in IgM is commonly found in PBC patients.

Due to an absence of a well validated scoring system for the diagnosis of PBC-AIH overlap, the criteria developed by Chazouillères *et al*[57] are commonly applied.

In various reports AIH-PSC overlap syndrome has been described and is characterised by ANA and/or SMA seropositivity, hypergammaglobulinaemia and interface hepatitis - all features typical of "classical" AIH - in conjunction with cholestatic biochemical changes, frequently associated with inflammatory bowel disease, and histological evolution to fibrous obliterative cholangitis, ductopenia, portal tract oedema and/or bile stasis[58].

DIAGNOSIS

The diagnosis is based on the combination of clinical and laboratory features and histological changes after exclusion of other causes of hepatitis[59].

Laboratory abnormalities

AIH is suggested by a patient with elevated Alanine-aminotransferase (ALT) and Aspartate transaminase (AST) activity, raised Immunoglobulin G (IgG), high titres of circulating antibodies, negative serum tests and exclusion of toxic hepatitis. However not all these laboratory findings need to be present in an individual patient.

Elevation of serum IgG is a common finding in AIH[60], but normal IgG levels may be found in up to 30% of patients[61,62].

Auto antibodies are the hallmark of AIH and can constitute an important part of the diagnostic work up. The classic antibodies associated with AIH are Antinuclear antibodies (ANA), anti-smooth-muscle antibodies (ASMA) and Anti Liver kidney microsomal (LKM-1). About 70%-80% of AIH patients have significant titres ($\geqslant$ 1:40) of ANA or ASMA and overall 3%-4% have anti LKM-1, while up to 20% are seronegative for these antibodies[60].

ANA are the most commonly found auto antibodies in AIH, yet are rather non-specific since they can be found in a large variety of diseases as well as in healthy individuals[63]. ANA may be the only antibody present or may occur in conjunction with ASMA. ASMA are the second major class of antibodies which have proved useful in the diagnosis of AIH. Although less prevalent than ANA they are more specific[64].

Autoantibody detection not only supports in the diagnosis but also classifies between type 1 and type 2 AIH. Type 1 AIH is associated with the presence of ANA and/or SMA and type 2 with the presence of anti-LKM-1 and/or anti-liver cytosolic-1 (LC-1). In Northern Europe and North America type 2 AIH accounts for less than 10% of all patients[55].

Antibodies to soluble liver antigen (SLA) or liver pancreas antigen (LP) are found in 10%-30% of patients with AIH. These antibodies are specific for AIH and may proof useful in the diagnosis[65]. Antibodies to actin and atypical peripheral anti-neutrophilic cytoplasm are also commonly seen in type 1 AIH, however their applicability is limited due to lack in specificity[59].

Liver histology

A liver biopsy is usually necessary to confirm the diagnosis, provide histological assessment of disease severity and exclude other causes of hepatitis. There are no individual histological criteria that prove the diagnosis of AIH[66]. Interface hepatitis (or piecemeal necrose) is the histological hallmark of AIH and is a process of inflammatory infiltration and erosion of the hepatic parenchyma at the junction of the portal

Table 3 Simplified diagnostic criteria for auto immune hepatitis[75]

Variable	Cutoff	Points
ANA or ASMA	⩾ 1:40	1
ANA or ASMA	⩾ 1:80	
or LKM-1	⩾ 1:40	2
or SLA	Positive	
IgG	> Upper normal limit	1
	> 1.10 times upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2
		⩾ 6: probable AIH
		⩾ 7: definite AIH

ANA: Antinuclear antibodies; ASMA: Anti-smooth-muscle antibodies; LKM-1: Anti Liver kidney microsomal; IgG: Immunoglobulin G.

tract[67]. It is found in 84%-98% of patients[13,45,68], but can also be seen in patients with drug-induced and viral hepatitis[68]. The infiltrates consist of hepatic mesenchymal cells containing lymphocytes, plasma cells and histiocytes that typically accompany these cells. Patients presenting with chronic AIH typically have plasma cells infiltrated at the interface and throughout the lobule. Plasma cells are not invariability present and paucity of plasma cells does not therefore exclude a diagnosis of AIH. They may be absent in up to one third of the patients[68,69].

In a recent study, emperipolesis and rosette formation appear superior histological predictors of AIH when compared to the typical histological features of interface hepatitis and plasma cells[70].

Diagnosis scoring system

Because there is no golden standard for the diagnosis of AIH, diagnostic scoring systems have been established that support the diagnosis in most of patients. The IAIHG scoring system, originally published in 1993[71] and revised in 1999[60], was developed as a search tool to ensure comparability of study populations. Despite a high degree of sensitivity (100%) and specificity (90%)[72-74], these criteria have been proven impractical in the day to day clinical practice.

In 2008 the IAIHG produced a simplified system for the diagnosis of AIH which is less complex and enhances applicability in clinical practice[75]. This system is based on four variables: presence and level of anti bodies, IgG concentration, typical histological features and absence of viral markers (Table 3). Recently three studies report that the simplified scoring system performs with high specificity (97%-99%) and lower sensitivity (81%-88%) when compared to the original diagnostic criteria yet requires further prospective validation[72,76,77].

TREATMENT

Indication of treatment

The short and long term efficacious of immune suppression in patients with AIH has been described unequivocally. When left untreated, an estimated 40% of patients will die within six months of diagnosis[78]. When treated adequately, the 20-year survival rate for all treated patients exceeds 80%, and life expectancy is similar to that of age and sex matched normal subjects from the same geographical area[79].

Updated treatment guidelines have recently been emerged by the European Association for the Study of the Liver (EASL) in 2015, the British Society of Gastroenterology in 2011 and the American Association for the Study of Liver Diseases (AASLD) in 2010[4,80,81]. Patients with AST levels 10-fold the upper normal limit, or fivefold the upper normal limit in concurrence with IgG levels at least twice the upper normal limit, or histological features of bridging necrosis or multiacinar necrosis, should be offered immunosuppressive treatment because of clear survival benefit (Table 4). Patients not satisfying these criteria must be personalized and treatment should be based on clinical judgement[4].

Standard treatment

Current therapeutic strategies for AIH consist of an induction with prednisone and frequently include subsequent addition of azathioprine (AZA) as steroid-sparing maintenance therapy[80]. Prednisone is introduced at a dose of 1 mg/kg with a maximum of 60 mg/d in monotherapy or a maximum of 30 mg/d in combination treatment[4,12]. After AST and ALT normalize, prednisone alone can be reduced by 10 mg/wk until a dose of 20 mg.

Patients treated with combination therapy can reduce prednisone by 5 mg/wk until 15 mg. A slower reduction is advised after this point[4,82]. For maintenance treatment AZA can be used at a dose 1-2 mg/kg per day either alone or in combination with low dose prednisone[4,83]. A recent review based on available randomised controlled trials found that prednisone monotherapy and prednisone in combination wit AZA are both feasible induction therapies for AIH, while maintenance therapy prednisone and AZA and Monotherapy AZA are superior to prednisone monotherapy[84]. AIH patients

Table 4 Indication for treatment of auto immune hepatitis (adapted from Manns *et al*[4])

Absolute	Relative
Serum AST ⩾ 10 fold ULN	Symptoms (fatigue, arthralgia, jaundice)
Serum AST ⩾ 5 fold ULN and IgG level ⩾ twice normal	Serum AST and/or IgG less than absolute criteria
Bridging necrosis or multiacinar necrosis on histological examination	Interface hepatitis

AST: Aspartate transaminase; ULN: Upper limit normal; IgG: Immunoglobulin G.

treated with corticosteroids and/or AZA have the risk of many side effects on both drugs. The side effects of long term treatment with corticosteroids are well known; acne, moon shape face, striae, weight gain and loss of bone density. Adverse effects of thiopurines are common and generally occur shortly after the start of therapy. They include allergic reactions, flu-like illness, nausea fever, malaise, rash, abdominal pain, hepatotoxicity, pancreatitis and myelosuppression[83,85-87]. The principal side effects of AZA are cytopenia and liver test abnormalities, which may be difficult to distinguish from inherent AIH disease activity.

Remission and relapse

Remission of previously symptomatic patients is defined as a complete normalisation of all inflammatory parameters, including AST, ALT, bilirubine, IgG, recovery from symptoms and inactive liver histology[4,9,82]. In 80%-90% of patients with moderate/severe AIH, serum ALT decreases after starting treatment. Usually a decrease is seen within two weeks. As transaminase decrease, clinical symptoms revolve and liver functions shows marked improvement within 3-6 mo after starting prednisone treatment either with or without AZA[81].

There is no prescribed duration of the length of treatment. Because histological restore lags behind clinical and biochemical improvement by 3-8 mo, treatment should be continued for at least this period[88,89]. Proper patient selection including sustained remission on immunosuppressive Monotherapy for a minimum of 2 years can markedly improve the success rate of treatment withdrawal[90]. The AASLD and EASL guidelines recommend treatment withdrawal, when serum liver and immunoglobulin levels have been repeatedly normal for a period of at least two years. Liver biopsy prior to termination of treatment is preferred[4,80]. Relapse is characterized by an increase in ALT levels (three times upper normal limit) and/or increase of serum IgG level to more than 2 g/L following tapering of steroid doses or after complete withdrawal of immunosuppression[4]. Literature from the 1970s showed a high risk of relapse after drug withdrawal[88,91], but this was later disputed and it was recommended that drugs withdrawal should be attempted[92]. A more recent retrospective analysis found that relapse occurred in almost all patients with AIH when immunosuppressive medication was discontinued or tapered[4,92,93]. Relapse occurred despite prior attainment of complete remission, including a histological inactive follow up biopsy prior to tapering in a subgroup of patients. In patients who have relapsed once, a subsequent attempt to withdrawal therapy was invariably associated with the re-occurrence of a relapse[93]. Since repeated relapses were associated with a poorer long term prognosis patients should receive life long treatment[94,95]. A lifelong follow up should occur in patients who successfully stopped immunosuppression, while a relapse can occur 10 years later[93].

Alternative treatment

In up to 10% of AIH patients, the therapeutic strategy of prednisone and AZA is unsuccessful, due to intolerable side effects or lack of clinical response[4,81]. In patients who fail on standard therapy, alternative immunosuppressive treatments have been tried with encouraging results. Cyclosporine[96-98], tacrolimus[99,100], methotrexate[101], cyclophosphamide[102] and mycophenolate mofetil[103-105] have been tried, with varying degrees of success, as a replacement for AZA.

In a small recent study allopurinol was added to the AZA or mercaptopurine treatment in patients who fail treatment due to ineffectiveness or intolerance, due to skewed thiopurine metabolism. The combination of low dose thioprines and allopurinol proved an effective and well-tolerated alternative in the treatment of AIH. Larger and controlled studies are needed to confirm these outcomes[106]. As an alternative for prednisone, budesonide is receiving considerable attention.

In two recent studies in patients with noncirrhotic AIH oral budesonide, in combination with azathioprine, induces and maintains remission. This treatment causes fewer steroid-specific side effects[107,108]. Routine use is not currently recommended, while the trial duration is short and the fact that no follow up date were presented[81]. AZA is the prodrug of 6-mercaptopurin (6-MP) and is converted into 6-MP in a nonenzymatic manner before exhibiting its antiproliferative and immunosuppressive properties. In patients with ulcerative colitis and Crohn's disease 6-MP has a beneficial role in AZA-intolerant patients[109]. In patients with AIH and AZA intolerance, 6-MP seems to be an effective and well-tolerated second line treatment[110]. The use of 6-thioguanine 6-TG), an agent more directly leading to down-stream active metabolites of AZA, showed clinical improvement in

three AIH patients intolerant to AZA. A prospective evaluation of 6-TG as possible immunosuppressive drug in AIH patients is warranted[111].

COMPLICATIONS AND PROGNOSIS

Complications in AIH are comparable to those seen in other liver diseases and in rare cases AIH presents by the occurrence of hepatic encephalopathy[112,113].

Liver fibrosis is often presence at diagnosis and a subgroup of patients have already cirrhosis at presentation[4,68] suggesting that the disease has gone unrecognized for a significant period prior to diagnosis. When left untreated, an etsimated 40% of patients will die within 6 mo of diagnosis[88,91,114]. In some patients without proper treatment, AIH progresses to cirrhosis and eventually Hepatocellular carcinoma (HCC). The presence of cirrhosis at diagnosis or during treatment and the need for long-term immunosuppressive therapy have been observed as risk factors for malignant transformation[115]. In addition risk factors for HCC furthermore include male gender, advanced stage disease, portal hypertension as ascites and esophageal varices[116]. HCC occurs in 1%-9% of AIH patients[116-118], which is less frequently compared to patients with chronic viral hepatitis[119]. Imaging with ultrasonography or computed tomography should be conducted every 6-12 mo. In patients who develop liver failure, liver transplantation needs to be considered[48,120]. When AIH is indicated for transplantation, transplanted patients, practically compared to other chronic liver diseases, have an excellent 5 year survival of between 78%-91%[121-123]. The recurrence rate of AIH after initial successful transplantation is problematic and occurs in around 30% of patients[124].

CONCLUSION

AIH is a relatively rare disease of unknown aetiology. Many factors contribute to the diagnosis, which is characterized by a female predominance, histologically evidence of periportal hepatitis in the absence of viral markers, hypergammaglobulinaemia, the presence of auto antibodies in serum, plasmacellular infiltrates and an optimal response to steroids in most patients. In AIH there is no existence of a pathognomonic feature and therefore the diagnosis rests on a combination of immunological, biochemical, and histological features together with exclusion of other liver diseases. Due to large heterogeneity of the disease, AIH might be unrecognised. The clinical manifestation of AIH can range from mild or severe symptoms to fulminant hepatic failure. AIH generally responds to immunosuppressive treatment and treatment is required as soon as the diagnosis is made. For most patients lifelong treatment is indicated. In patients in whom all treatment attempts fail liver transplantation needs to be considered.

AIH remains a major diagnostic and therapeutic challenge. Growing insights into the clinical presentation of AIH highlights the importance of evaluation of the current diagnostic criteria, role of genetic and environmental factors, as well as the development of new treatment strategies.

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