DOI: 10.15825/1995-1191-2022-2-39-50

HISTORICAL ASPECTS AND CURRENT UNDERSTANDING OF AUTOIMMUNE HEPATITIS. WHEN IS LIVER TRANSPLANTATION INDICATED? (REVIEW)

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Autoimmune hepatitis (AIH) can occur at any age and is more common in women. The disease is a manifestation of autoimmune predisposition caused in genetically susceptible people exposed to certain environmental factors. The pathogenetic mechanism of AIH is not yet fully understood, but it involves an aggressive cellular immune response. The pathogenesis and severity of AIH also depend on various cytokines. This disease is characterized by elevated levels of transaminases – aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Liver histology plays a crucial role in confirming or supporting the clinical diagnosis of AIH. Diagnosis of AIH remains a challenge in clinical practice. AIH is one of the few liver diseases for which pharmacologic treatment has been shown to improve survival. Standard treatment is based on high-dose prednisone alone or prednisolone plus azathioprine. It leads to disease remission in 80%-90% of patients. Approximately 20% of patients do not respond to the standard steroid treatment and are treated with second-line immunosuppressive drugs: mycophenolate mofetil, budesonide, cyclosporine, tacrolimus, everolimus, and sirolimus. There have been reports on the use of infliximab and rituximab. In the natural course of AIH and resistance to therapy, there is a tendency for cirrhosis to develop and for the disease to progress to an end stage. These patients, as well as those diagnosed with fulminant liver failure, require liver transplantation.

Keywords: autoimmune hepatitis, AIH, pathogenesis, histology, treatment.

In 1950, the first description of hepatitis was published by Jan Waldenström. The disease was later to be called "autoimmune hepatitis" only in 1992. It has been previously referred to by various terms, most commonly "autoimmune chronic active hepatitis" [1]. Autoimmune hepatitis (AIH) is a rare liver disease [2–6] that occurs in children and adults of all ages and is characterized by progressive inflammatory hepatopathy [7]. Webb et al. [8] defined AIH as an uncommon idiopathic syndrome of immune-mediated destruction of hepatocytes, typically associated with autoantibodies. AIH can lead to acute liver failure [1], or the disease can become chronic and lead to an end-stage condition requiring liver transplantation [1, 2, 7].

Classification of autoimmune hepatitis. There are currently two main forms of AIH. Type 1 AIH is characterized by smooth muscle antibodies, antinuclear antibodies, or both, whereas Type 2 AIH is characterized by anti-liver/kidney microsomal antibodies, and anti-liver cytosol 1 antibodies, or both [4, 9]. Previously, there was a third form of AIH in which there are antibodies to soluble liver antigen (SLA-positive AIH). Later, it was found that SLA can be present in type 1 AIH and in cryptogenic cirrhosis. Immunoglobulin G4(IgG4)-related AIH recognized as a new disease [10].

Epidemiology of autoimmune hepatitis. AIH can occur at any age [7]. The average age of adult AIH patients is 58.6 years [11]. AIH incidence peaks around the age of 70 at diagnosis in both men and women. The incidence is lower at younger ages. In Japan, AIH incidence in both sexes peaks around age 60 [12]. However, AIH is more common in women than in men [4, 7, 13, 14]. Among the adult population, women are more frequently affected than men by a ratio from 3 : 1 to 8 : 1. A study by Abe et al. [11] found that the ratio of women to men suffering from AIH was 9 : 2. AIH mostly affects young women.

According to Werner et al. [15], AIH is a fairly uncommon disease in the Swedish population. Its incidence was 0.85 per 100,000 population, and 76% of the cases were females. Women had a peak after menopause, whereas men had a peak in the late teens. Autoantibodies indicative of AIH type 1 were found in 79% of cases. Almost half of the patients (49%) had other concomitant autoimmune diseases.

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L. Grønbæk et al. [16] identified AIH patients (n = 1721) from Danish nationwide health registries diagnosed from 1994 to 2012. The incidence rate was 1.68 per 100,000 population per year, and it doubled during the study period. Of the 1,318 patients who were biopsied at diagnosis, 28.3% had cirrhosis. In the first year after diagnosis, AIH patients had six-fold higher mortality than the general population; later, their mortality remained two-fold higher. Their 10-year cumulative mortality was 26.4% (95% CI 23.7 to 29.1). About 38.6% of deaths were liver-related.

In 2015, a nationwide survey of AIH patients in Japan (n = 1,682) diagnosed from 2009 to 2013 in 437 hospitals and clinics. The mean age at diagnosis was 60.0 years. Women (87.1%) were prevalent among the patients. Serum immunoglobulin G levels were high, peaking at 1.5–2.0 g/dL. Histological diagnosis of acute hepatitis, chronic hepatitis, and cirrhosis were seen in 11.7, 79.6, and 6.7% of patients respectively. In addition to elevated aminotransferase levels, the frequencies of emperipolesis and human leukocyte antigen (HLA)-DR2 positivity were higher in patients with acute hepatitis than in those with chronic hepatitis. Approximately 80% of patients were treated with corticosteroids, and in 97.7 % of them, their condition improved. Steroid pulse therapy was more frequently given to patients with acute hepatitis than to those with chronic hepatitis [12].

AIH prevalence and incidence are lower in the Asia-Pacific than in Europe and America. In Singapore and Brunei, the prevalence is 4–5 per 100,000 population, in Europe it is 10–20 : 100,000, and in Alaska it is as high as 43 : 100,000. European and American patients seem to have more severe disease, characterized with human leukocyte antigen-DR3 haplotype, younger age, more AIH-induced "cirrhosis" at diagnosis, higher elevated serum IgG levels [17].

Etiology of autoimmune hepatitis. The cause of AIH remains unknown [18], although both genetic and environmental factors are involved [3, 4, 7]. In other words, the disease is a manifestation of an autoimmune predisposition in genetically susceptible individuals exposed to likely environmental factors [19].

The liver is constantly exposed to a large number of different antigens: pathogenic infectious agents, toxins, tumor cells, food antigens and others. The liver's loss of tolerance to its own antigens can lead to AIH. The current paradigm states that the disease occurs in genetically susceptible subjects as a result of autoimmune processes caused by unknown factors, among which may be infections, chemicals and drugs. The disease etiology includes a clear association with: 1) HLA variants, 2) other non-HLA gene variants, 3) female sex, and 4) environment [8].

Risk factors for autoimmune hepatitis. Predictors of AIH are not clearly defined, but a genetic predisposition to AIH has been established for a relatively long time. AIH is not inherited in a Mendelian autosomal dominant, autosomal recessive, or sex-linked fashion. The mode of inheritance of the disorders is unknown and involves disruption of one or more genes working independently or together [20].

In AIH type 1, genetic predisposition is determined by a strong association with HLA antigens DRB1*0301 and DRB1*0401. In addition, the gene encoding cytotoxic T lymphocyte antigen-4 (CTLA-4) on chromosome 2q33 may also affect autoimmunity [21]. Similarly, both Europe and North America have a predisposition to AIH type 1 in individuals with HLA antigens DR3 (DRB1*0301) and DR4 (DRB1*0401). In a study of Japanese patients with type 1 AIH, all were found to have DRB1 alleles which encode histidine at position-13.

The predisposition to AIH type 2 is transmitted through HLA antigens DR7 (DRB1*0701) and DR3 (DRB1*0301). The disease is more aggressive and has a worse outcome in patients with DRB1*0701 antigens [22].

Not only genes of the major histocompatibility complex play an important role in autoimmune processes, but also genes involved in immune regulation and preservation of immune homeostasis, in particular those involved in apoptosis. According to K. Agarwal et al. [21], polymorphism of the Fas gene at position -670 does not influence susceptibility to AIH, but may affect the early development of cirrhosis. Cirrhosis at presentation was more common in patients with the adenosine/adenosine or adenosine/guanine genotypes than in those with the guanine/guanine genotype (29% versus 6%).

Pathogenesis of autoimmune hepatitis. The mechanism of the emergence and development of AIH is not fully understood, but it involves an aggressive cellular immune response [20]. Under the influence of yet unknown triggers, the mechanisms regulating immunity are violated. As a result, a pathological immune response, mediated by T-cells and directed against liver autoantigens, develops [23]. Immune reactions are inadequately controlled by damaged regulatory T cells [4]. Therefore, quantitative and functional defects in regulatory T cells play a crucial role in the onset and persistence of autoimmune liver injury in AIH [7, 8].

Various cytokines influence the pathogenesis and severity of AIH [24]. The complex interaction between proinflammatory cytokines and Th17 cytokines, as well as Treg IL-12p40 suppression are thought to play a central role in AIH pathogenesis. Serum IL-21 levels are significantly elevated in severe AIH cases compared to mild cases. Serum IL-21 levels positively correlate positively with total bilirubin levels and grading of necroinflammatory activity in liver biopsies [11].

Interleukin-33 (IL-33), which has proinflammatory activity, and its soluble ST2 (sST2) receptor, are involved in the pathogenesis of many autoimmune diseases. In the liver, IL-33 is secreted by hepatocytes and vascular

endothelial cells, including sinusoids. Their serum levels are significantly higher in AIH patients than in healthy individuals and in patients with other autoimmune diseases. Serum IL-33 and sST2 levels are significantly higher in acute-onset AIH than in chronic-onset AIH [18]. Serum IL-33 levels in patients with acute-onset AIH positively correlate with markers of hypergammaglobulinemia (IgG, IgM and IgA), liver injury (gamma glutamyltransferase and alkaline phosphatase) and proinflammatory cytokine levels (IL-17A and IL-4) [25]. Serum IL-33 and sST2 levels in AIH patients positively correlate with serum total bilirubin, ALT, and noninflammatory activity, but negatively correlate with serum albumin and prothrombin time. In AIH patients responding to prednisolone treatment, serum IL-33 and sST2 levels are significantly reduced after treatment. Interestingly, high serum IL-33 levels were associated with a significantly higher risk of recurrence [18]. The authors came to the following conclusions: 1) IL-33 and sST2 play an important role in the pathogenesis and severity of AIH; 2) they may be a promising target for AIH therapy.

Biochemical changes. AIH is characterized by elevated levels of transaminases [3–5]: AST and ALT [14]. Regardless of age, gender, or ethnicity, AIH can be suspected in patients with unexplained elevated liver enzymes and/or cirrhosis. Serum aminotransferase levels in AIH patients vary widely, and autoantibodies are not consistently present [26].

Immunological manifestations. In AIH, organ-specific and nonorgan-specific autoantibodies are present in the blood serum, and there is increased IgG levels [3–6, 14, 23]. According to Kim et al. [13], antinuclear antibodies, smooth muscle antibodies and hepatic/renal microsomal antibodies were present in 94.2%, 23.0% and 2.9% of AIH patients, respectively.

In acute presentation, in contrast to chronic AIH, there are often atypical immunoserological manifestations [27]. Thus, IgG levels may remain within the normal range. According to Lohse and Mieli-Vergani [28], 5% to 10% of patients with AIH have normal IgG levels at the time of diagnosis. In another study [26], 39% (27/70) of AIH patients also had normal IgG levels. According to the authors, this suggests that many AIH patients have atypical manifestations of the disease. In these patients, AIH can only be diagnosed if, in addition to a high autoantibody titer, there is a histological pattern "typical" of the disease. Therefore, close collaboration between hepatologists and pathologists is crucial for the accuracy of AIH diagnosis [27].

In AIH, T helper cells (T(H)0) are activated. In the presence of interleukin 12 (IL-12) or IL-4, T(H)0 lymphocytes can differentiate into T(H)1 cells, which play a leading role in macrophage activation. Increased HLA class I expression makes liver cells vulnerable to attack by CD8 T cells and induces expression of HLA class II hepatocytes. In addition, T(H)1 cells can differentiate into T(H)2 cells that produce IL-4, IL-10, and IL-13. These cytokines promote antibody production by B-lymphocytes. Recognition of autoantigens is tightly controlled by regulatory mechanisms, such as CD4+CD25 regulatory T cells. Thus, AIH is characterized by a quantitative and functional disruption of regulatory T cells, leading to preservation of effector immune responses followed by persistent liver destruction [29, 30].

AIH increases the number of follicular helper T (Tfh) cells expressing interleukin IL-21 in peripheral blood. IL-21 member of the type-I cytokine family. This interleukin exerts various effects on the immune system, including B cell activation, plasma cell differentiation, and immunoglobulin production. The level of IL-21 was found to be significantly elevated in the serum of patients with AIH compared with other liver diseases and controls ($P < 0.0001$). Moreover, the higher the level was, the more severe AIH was ($P < 0.05$). In addition, serum IL-21 levels correlated positively with total serum bilirubin levels ($p < 0.05$), grading of necroinflammatory activity in AIH patients ($p < 0.005$) and negatively correlated with serum albumin levels ($p < 0.05$). In patients with biochemical remission of AIH, serum IL-21 levels remained elevated and correlated positively with serum IgG levels ($p < 0.01$). significantly higher than that in healthy volunteers [11]. The authors conclude that IL-21 may play an important role in the pathogenesis of AIH, and may represent a promising target for AIH therapy.

Autoimmune hepatitis is associated with a predominance of T helper 1 (Th1) expression and a decrease in the number and function of regulatory T cells (Tregs). The role of circulating activated Tfh and plasma cells in the pathogenesis of AIH is associated with hypergammaglobulinemia [31].

Pathomorphology. Liver histology is critical in diagnosing AIH, especially when using simplified IAIHG criteria [32]. According to some investigators [33], biopsy for AIH can be excluded in patients with other clinical criteria for the disease. However, liver biopsy currently remains mandatory for AIH diagnosis [34]. In addition, liver biopsies are performed to monitor the effectiveness of therapy and to determine further treatment strategy.

The most typical, but non-specific pathohistological finding in AIH is the presence of borderline hepatitis (also called interface hepatitis), in which there is inflammation not only of the portal tract, but also of the periportal parenchyma, with its infiltration by lymphocytes, plasma cells and macrophages [3, 4, 6, 14, 18, 23]. The lymphocytic inflammatory infiltrate contains a large number of CD4+ T cells [8]. The high content of plasma cells in the inflammatory infiltrate is also one of the main histological indicators of AIH. In severe and progressive disease, centrilobular lesions and necrosis as well as bridge necroses are present.

In a study by Sandler et al. [35], 96% (79/82) of AIH patients had morphological signs of borderline hepatitis

with infiltrates consisting of lymphocytes and plasma cells; in addition, emperiopoiesis was diagnosed in 60% (49/82) and rosette formation in 23% (19/82).

Necrosis of hepatocytes leads to liver fibrosis [8]. Liver fibrosis and cirrhosis can occur even in the subacute course of the disease [28]. At diagnosis, almost 30% of patients already have cirrhosis [36], and in a study by Abe et al. [11] – only 18.2%. In AIH, corticosteroid treatment leads to partial restoration of liver morphology in 53–57% of patients. Fibrosis progression is slowed or prevented in 79% of patients. If it is not possible to completely suppress inflammatory activity within 12 months, cirrhosis continues to progress in 54% of patients, and results in death or requirement for liver transplantation in 15% [37]. Despite treatment, almost half of patients (46%) still have histological activity of AIH amid improved biochemical parameters [38].

In acute presentation of AIH, in contrast to chronic AIH, there are often atypical histological manifestations [27, 34]. Chronic AIH is histologically characterized by borderline hepatitis, plasma cell infiltration and centrilobular necrosis. Acute AIH is not significantly different histologically from chronic AIH. However, histological active findings such as lobular inflammation, macrophages and focal necrosis or single cell necrosis were significantly more frequent in patients with acute presentation of AIH, whereas portal fibrosis was significantly more frequent in patients with chronic AIH [27]. Based on pathohistological findings, the authors believe that almost all cases of acute presentation of AIH might be exacerbations of non-symptomatic pre-existing chronic AIH.

The diagnostic criteria commonly used for classical chronic AIH are generally applicable to acute exacerbation, but acute-onset AIH may present with additional pathological features – centrilobular necrosis. However, centrilobular necrosis is also a feature of drug-induced liver injury, and there are no known histological characteristics to differentiate drug-induced liver injury from acute-onset AIH. Moreover, immune-mediated drug-induced liver injury makes diagnosis even more difficult [34].

Importantly, immunohistochemical studies have revealed high expression of IL-33 in liver slices from AIH patients. IL-33 expression in AIH is concentrated in the inflammation areas and is observed in the sinusoidal endothelial cells and other vessels, but was not detected in intrahepatic bile ducts [18].

Immunohistochemical phenotyping of inflammatory cells in the liver shows a predominance of T cells. Among them, the majority were CD4 helper/inducer cells, and the number of CD8 cytotoxic/suppressor cells was negligible. In addition, natural killers, monocytes/macrophages, and B-lymphocytes were present in the infiltrates [8, 29].

The simplified score is a reliable and simple tool for diagnosing AIH. However, both systems cannot unmask autoimmune hepatitis component efficiently in AIH patients with concurrent autoimmune or non-autoimmune liver diseases [39]. According to the authors, their study also strongly reiterates the importance of liver biopsy when examining patients.

Autoimmune hepatitis and malignancies. Patients with AIH have a high risk of malignant tumors due to immunological abnormalities, use of immunosuppressive agents and chronic inflammation. Grønbæk et al. [16] found that the 10-year cumulative risk of hepatocellular carcinoma in AIH was 0.7%. Male gender and cirrhosis were associated with high mortality and development of hepatocellular carcinoma. 3.6% of deaths were from hepatocellular carcinoma. Even higher rates of malignant tumors in AIH are given by Arinaga-Hino et al. [40]. In their study, of 256 patients suffering from AIH, 27 (10.5%) developed malignancies; 11 (4.3%) with hepatobiliary cancer and 16 (6.3%) with extrahepatic malignancies. The risk factors for hepatobiliary cancer at the diagnosis of AIH were low levels of alanine aminotransferase ($P = 0.0226$), low platelet counts ($P < 0.0001$), and cirrhosis ($P = 0.0004$). The risk factor for extrahepatic malignancy was relapse of AIH ($P = 0.0485$).

Diagnosis. In 1993, the International Autoimmune Hepatitis Group (IAIHG) codified diagnostic criteria to identify patients with having either probable or definite AIH for research purposes [41]. In 1999, the IAIHG revised the descriptive diagnostic criteria to optimize AIH diagnosis in individuals with atypical manifestations of the disease as well as to improve the accuracy of excluding cholestatic autoimmune liver diseases (primary biliary cirrhosis and primary sclerosing cholangitis). As a result of the revision, the specificity of the criteria was improved to 90%. The revised criteria also showed very good efficacy in patients with few or atypical signs of AIH [42]. However, the diagnostic criteria for AIH remained complex, with 13 components and 29 possible classes, which limited their application in routine clinical practice. Therefore, a simplified scoring system for diagnosing AIH in routine clinical practice was developed in 2008 [43, 44]. These criteria consist of only four available parameters: liver histology, autoantibody titers, IgG level, and exclusion of viral hepatitis (Table). Out of a total of eight points, a probable diagnosis of AIH is made at six points, and a definite diagnosis of AIH is made at seven or eight points. The simplified criteria were originally defined and validated in a retrospective cohort study involving 11 international centers from the Americas, Europe, and Asia [44]. In this study, response to immunosuppressive therapy was also mandatorily included in all AIH patients. Subsequently, the AIH diagnostic simplified system was used in numerous other studies [32, 39, 45–51].

Table

Simplified diagnostic criteria for AIH (according to Hennes et al. [44])

Variable	Cutoff	Points
ANA or SMA	≥1 : 40	1
ANA or SMA	≥1 : 80	2
or LKM	≥1 : 40	
or SLA	Positive	
IgG	> Upper normal limit	1
	>1.10 times upper normal limit	2
Liver histology	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2

Note. ANA, antinuclear antibodies; SMA, smooth muscle cell antibodies; LKM, liver-kidney microsomal antibodies; SLA, soluble liver/liver-pancreas antibodies. ≥6: probable AIH; ≥7: definite AIH.

Hennes et al. [44] (2008) reported 88% sensitivity and 97% specificity for the diagnosis of probable AIH (≥6 points) and 81% sensitivity and 99% specificity for the diagnosis of definite AIH (≥7 points). Several other studies have confirmed the sensitivity and specificity of a simplified scoring system for the diagnosis of AIH in American [37], Mexican [52], and Korean [13] patients. In these studies, sensitivity and specificity of detecting a probable AIH ranged from 65% to 95% and from 90% to 98%, respectively, while sensitivity and specificity of detecting a definite AIH ranged from 15% to 87% and 99% to 100%, respectively. Using simplified criteria, H. Wobser et al. [26] determined the overall sensitivity and specificity of detecting a probable AIH (score ≥6) to be 96% and 97%, respectively. For diagnosis of definite AIH (scores ≥7), the sensitivity and specificity were 43% and 100%.

In a study by Qiu et al. [32], the simplified criteria had sensitivity and specificity of 90% and 95%, respectively, for the diagnosis of probable AIH in Chinese patients. This compares well with the more stringent revised original criteria, which had sensitivity and specificity of 100% and 93%, respectively, for probable AIH. In addition, the predictability of the revised original criteria and simplified criteria were 96% and 94% for probable AIH, and 88% and 87% for definite AIH, respectively. The authors concluded that the simplified criteria are highly sensitive and specific for the diagnosis of AIH in Chinese patients.

AIH may have cholestatic features that are outside the codified diagnostic criteria. Patients with AIH may have antimitochondrial antibodies and coincidental bile duct injury or loss (2%–13% of patients), focal biliary strictures and dilations based on cholangiography (2%–11%), or histologic changes in bile duct injury or loss in the absence of other features (5%–11%). These findings probably represent atypical manifestations of AIH or variants of primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC), depending on the predominant findings. Serum levels of alkaline phosphatase and γ-glutamyl transferase, histologic features of bile duct injury, and findings from cholangiography are associated with responsiveness to corticosteroid therapy and individualized alternative treatments [37].

Rapid diagnosis and initiation of immunosuppressive treatment are necessary for both acute exacerbation and acute-onset to prevent fatal liver failure [34]. However, the diagnosis of acute AIH with atypical features remains a difficult challenge; authors believe that the revised original scoring system has shown better results in patients with acute-onset AIH than the simplified system [46]. Li et al. [47] also note that the revised scoring system has better performance in diagnosing AIH patients than the simplified scoring system. Many chronic liver diseases can coexist with AIH [53, 54]. Therefore, correct and timely diagnosis of AIH remains a challenging problem in clinical practice [26].

Overlap syndrome. The so-called "overlap syndrome" has long been recognized, in which there are signs of two autoimmune liver diseases, for example, AIH and PBC or PSC [55]. Patients with a combination of AIH and primary biliary cirrhosis suffered from a more aggressive form of PBC [28]. Combined therapy with ursodeoxycholic acid and low-dose immunosuppressive drugs was effective in these patients.

Overlap between AIH and PSC is rare, especially with the new scoring system. Of 147 patients with PSC, the simplified scoring system identified two patients with probable AIH, demonstrating the high specificity of this system [56].

Differential diagnosis. To make a diagnosis of AIH, PBC and PSC must first be excluded, and then such diseases as chronic viral hepatitis, Wilson–Konovalov disease, Alpha-1 antitrypsin deficiency, hemochromatosis, drug-induced hepatitis, alcoholic hepatitis, nonalcoholic fatty liver disease, etc. It is particularly important to distinguish AIH from other forms of chronic hepatitis because most patients respond to anti-inflammatory and/or immunosuppressive therapy [57].

Clinic. AIH is an inflammatory liver disease with a wide range of clinical manifestations [58], ranging from subclinical to fulminant hepatitis [6] or from isolated acute or chronic hypertransaminasemia to acute liver failure [4, 59, 60]. A study by Kim et al. [13] AIH patients reported that 30.6% were asymptomatic, 22.7% were cirrhotic, and 4.3% displayed hepatic decompensation. In most cases, AIH with acute presentation is merely acute exacerbation of classical chronic AIH, but pure acute-onset AIH without previous symptoms of chronic liver disease is also encountered [34]. In acute presentation, in contrast to chronic AIH, there are often atypical clinical manifestations [12, 61].

AIH has diverse clinical phenotypes and outcomes in ethnic groups within a country and between countries,

and these differences may reflect genetic predispositions, indigenous etiological agents, pharmacogenomic mechanisms and socioeconomic reasons. In the United States, African-American patients have cirrhosis more commonly, treatment failure more frequently and higher mortality than white American patients. Survival is poorest in Asian-American patients. AIH in other countries is frequently associated with genetic predispositions that may favor susceptibility to indigenous etiological agents. Acute-on-chronic liver disease increases mortality and socioeconomic and cultural factors affect prognosis. Ethnic-based deviations from classical phenotypes can complicate the diagnosis and treatment of AIH in non-white American populations [62].

Therapy. AIH is one of the few liver diseases for which pharmacologic treatment has been shown to improve survival [3, 57, 58]. Non-specific immunosuppression is the current standard therapy [8], which is prescribed immediately after diagnosis [4, 63] and which prevents rapid deterioration and promotes remission and long-term survival [64]. The treatment not only can prolong patients' lives, but also improve their quality of life and avoid liver transplantation [57]. Response to steroid treatment is considered as an additional criterion in the diagnosis of AIH [3, 26]. Lack of response to steroids is grounds for revision of the diagnosis [23].

Standard treatment regimens include high-dose prednisolone alone or prednisolone plus azathioprine [19, 23]. Positive effects with steroid treatment are observed in 75%–90% of patients [3, 23]. However, approximately 20% of patients do not respond to steroid treatment, and second-line immunosuppressive medications are used for their treatment. These drugs are also used in patients who cannot tolerate standard therapy. Second-line drugs include mycophenolate mofetil, budesonide, cyclosporine, tacrolimus, everolimus, and sirolimus. However, there have been no randomized controlled trials of the efficacy of second-line drugs in the treatment of AIH. Mycophenolate mofetil is the most widely used second-line drug; it is particularly effective in patients with azathioprine intolerance. Experience with infliximab and rituximab has been published. However, there is a high risk of infectious complications when treated with these drugs [5, 23].

Treatment of AIH with various immunosuppressive drugs is aimed at minimizing liver inflammation [65–67], which reduces the risk of fibrosis progression and cirrhosis development, hence reducing the need for liver transplantation [68].

Current studies aimed at restoring the regulatory function of T cells in vitro to acquire tolerance in vivo have shown promising results [4]. Further elucidation of the cellular and molecular pathways involved in the pathogenesis of AIH is likely to lead to the discovery of new, adaptable and better tolerated therapies [8; 23].

In the natural course of AIH, there is a tendency for liver cirrhosis [69] and progression to end-stage disease [19]. Resistance to therapy also leads to end-stage liver disease. These patients, as well as those found to have fulminant liver failure at diagnosis, require liver transplantation [2, 64, 70].

Outcomes. Without treatment, the prognosis is poor [5, 23], often leading to cirrhosis, liver failure, and patient death [36, 71–73]. The presence of cirrhosis at diagnosis of AIH, lack of response to initial immunosuppressive therapy or elevated international normalized ratio were associated with poor outcome and requirement for liver transplantation [7]. Otherwise, most deaths were associated with liver failure, shock, or gastrointestinal bleeding [71]. In contrast, Ngu et al. [74] (2013) suggest that histological cirrhosis at diagnosis is not associated with poor prognosis and does not influence the response to initial immunosuppressive treatment. According to these authors, incomplete normalization of ALT at 6 months, low serum albumin concentration at diagnosis, and age at presentation of ≤20 years or >60 years were significant independent predictors of liver-related death or requirement for liver transplantation.

CONCLUSION

The term "autoimmune hepatitis" was coined in 1992. There are currently two main forms of AIH. Type 1 AIH is characterized by smooth muscle antibodies, antinuclear antibodies, or both, whereas Type 2 AIH is characterized by anti-liver/kidney microsomal antibodies, and anti-liver cytosol 1 antibodies, or both. Autoimmune hepatitis can occur at any age and is more common in women than in men. The disease is a manifestation of an autoimmune predisposition caused in genetically susceptible people exposed to certain environmental factors. The pathogenetic mechanisms of AIH are not yet fully understood, but it involves an aggressive cellular immune response. The main role is attributed to defects in regulatory T cells. Various cytokines also influence the pathogenesis and severity of AIH. This disease is characterized by elevated levels of transaminases: AST and ALT.

Liver histology plays a crucial role in confirming or supporting the clinical diagnosis of AIH. The most typical, but non-specific pathohistological finding in AIH is the presence of borderline hepatitis, in which there is inflammation not only of the portal tract, but also of the periportal parenchyma, with its infiltration by lymphocytes, plasma cells and macrophages. The lymphocytic inflammatory infiltrate contains a large number of CD4+ T cells. The high content of plasma cells in the inflammatory infiltrate is one of the main histological indicators of AIH. In severe and progressive disease, centrilobular lesions and necrosis as well as bridging necrosis are present. Hepatocyte necrosis leads to liver fibrosis and cirrhosis. Acute presentation

of AIH often has atypical histological manifestations in the form of centrilobular necrosis. Immunohistochemical studies revealed high expression of IL-33 in areas of inflammation, which is observed in the sinusoidal endothelial cells and other vessels. Phenotyping of inflammatory cells in the liver showed a predominance of CD4 helper/inducer cells, while the number of CD8 cytotoxic/suppressor cells was insignificant. Besides, natural killer cells, monocytes/macrophages, and B-lymphocytes were present in the infiltrates. Patients with AIH had a high risk of malignancies due to immunological disorders, use of immunosuppressive agents and chronic inflammation. AIH may have cholestatic features that are outside the codified diagnostic criteria. Rapid diagnosis and initiation of immunosuppressive treatment are necessary for both acute exacerbation and acute onset to prevent fatal liver failure. However, the diagnosis of AIH remains a challenging problem in clinical practice.

AIH is one of the few liver diseases for which pharmacologic treatment has been shown to improve survival. Standard treatment regimens include high-dose prednisone alone or prednisolone plus azathioprine. Approximately 20% of patients do not respond to steroid treatment and are treated with second-line immunosuppressive drugs: mycophenolate mofetil, budesonide, cyclosporine, tacrolimus, everolimus, and sirolimus. In the natural course of AIH and resistance to therapy, there is a tendency for cirrhosis to develop and for the disease to progress to an end stage. These patients, as well as those with fulminant liver failure at diagnosis, require liver transplantation.

The authors declare no conflict of interest.

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The article was submitted to the journal on 3.03.2022