Review Article

CLINICAL INVESTIGATION

Autoimmune hepatitis: Risk factors, pathophysiology, diagnosis and management

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Abstract

Autoimmune hepatitis is characterized as an entity of chronic hepatitis that must be distinguished from chronic viral hepatitis, drug-induced and alcohol-induced hepatitis and idiopathic chronic hepatitis. The pathogenesis of autoimmune hepatitis is very complex and includes interactions between the tolerant liver, environmental triggers, and dysregulated immunological mechanisms. The immune response in autoimmune hepatitis is likely induced by the presentation of self-antigens to uncommitted naive $CD4^+$ T Helper cells (TH0). Liver biopsy is considered the gold standard for assessing liver fibrosis in patients with autoimmune hepatitis. The objective of autoimmune hepatitis treatment is complete biochemical and histological remission, with minimum side effects of treatment, preventing fibrosis progression. Primary treatment involves steroid induction therapy, where the choice is based on histological severity and the fibrosis stage, followed by maintenance therapy with a steroid-sparings agent.

Keywords: Autoimmune hepatitis • Risk factors • Pathophysiology • Management • Diagnosis

Abbreviations: Alanine Aminotransferase (ALT), Antigen-Presenting Cells (APCs), Aspartate Aminotransferase (AST), Autoimmune Hepatitis (AIH), Anti-Nuclear Antibodies (ANA), Human Leukocyte Antigen (HLA), Immunoglobulin G (IgG), Anti-Liver-Kidney Microsomal Antibody Type One (LKM1), Anti-Liver Cytosol Type 1 Antibody (LC1), Major Histocompatibility Complex (MHC), Primary Biliary Cholangitis (PBC), Primary Sclerosing Cholangitis (PSC), Anti-Smooth Muscle Antibodies (SMA).

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Introduction

Autoimmune Hepatitis (AIH) is a chronic and progressive inflammatory liver disease described by elevated serum aminotransferases and Immunoglobulin G (IgG), the availability of autoantibodies, and interface hepatitis with lymphoplasmacytic infiltration in liver histology. It is explained by the availability of interface hepatitis and portal plasma cell infiltration on histologic examination, hypergammaglobulinemia, and autoantibodies [1, 2]. AIH is can be characterized histologically by interface hepatitis and lymphocytic infiltration of the liver and, serologically by elevated levels of Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Immunoglobulin G (IgG), and the presence of autoantibodies [3]. Autoimmune Hepatitis (AIH) is considered immune disorder-induced liver damage mediated by abnormal activation of immunocytes and the generation of pro-inflammatory mediators [4].

Risk factors

The pathogenesis of AIH is very complex and includes interactions between the tolerant liver, environmental triggers, and dysregulated immunological mechanisms [5, 6]. The risk factors of AIH are discussed below:

Genetic predisposition

Genetic factors influence an individual's vulnerability to advance AIH. Genetic studies have revealed that predisposition to advancing AIH can be attributed in part to polymorphisms of the Human Leukocyte Antigen (HLA) region, encoding the Major Histocompatibility Complex (MHC). The prominent predisposing function of genes encoded in the HLA region has been verified in the largest genome-wide correlation survey performed to date in AIH. The HLA genotypes vary between different ethnic groups and geographical regions [7].

Sex and age

One feature of population studies of AIH that has been almost universal in a female preponderance. AIH affects mainly women, although 25%-30% of patients are male. Irrespective of subtype, 75% -80% of patients with AIH are women, a characteristic common to most autoimmune diseases. According to the antibody profile, AIH can be categorized into two subtypes, type one AIH (AIH-1) is described by the availability of ANAs and/or Anti-Smooth Muscle Antibodies (SMA) while type two AIH (AIH-2) Anti-Liver-Kidney Microsomal Antibody Type One (LKM1), anti-LKM3 and/or Anti-Liver Cytosol Type 1 Antibody (LC1) are the markers of the disease. AIH-1 affects people of all ages with two peaks, one in childhood or adolescence between 10 years and 18 years of age and the other in adulthood around the age of 40 years. Only 20% of patients are diagnosed after the age of 60 years. AIH-2 mainly affects children, involving infants [8, 9].

Viruses and the microbiota

Most currently, environmental factors (such as viral infections) have also been implicated in the advancement of AIH. The intestinal microbiota is perhaps included in the pathophysiology of AIH. For example, alterations in the composition of the intestinal microbiota (dysbiosis) in terms of decreased diversity and lowered total load of gut bacteria have been explained in experimental models of AIH. Compared with healthy volunteers, AIH seems to be correlated with dysbiosis due to reduced availability of anaerobic bacteria in the gut, elevated gut permeability and accelerated translocation of intestinal microbial products into the systemic circulation. Several viruses have been correlated with the advancement of autoimmune hepatitis, such as hepatitis A, hepatitis C, hepatitis E, measles, Epstein-Barr, and herpes simplex viruses. The only known bacterial genus correlated with AIH is Rickettsia, as one of its proteins drives an autoimmune response mediated by $CD4^+$ T cells [10-12].

Medications

Several pharmaceutical agents that cause autoimmune hepatitis are minocycline, nitrofurantoin, isoniazid, alpha-methyldopa, tienilic acid, pemoline, melatonin, ornidazole, diclofenac, propylthiouracil, and statins. Herbal remedies, such as dai-taiko-so (da chai hu tang; commonly used in Japan), have also been correlated with the disorder [13]. Acute liver failure attributed to drugs, one of the initial causes of liver failure, can reveal autoimmune manifestations identical to idiopathic AIH. Drug-induced AIH is classified separately from idiopathic AIH; however, medications cannot be completely ruled out as possible causative agents of AIH even in the absence of a clear relationship with the uptake of the medicine. Unrecognized previous exposure and sensitization to medicines could be responsible for the induction or maintenance of liver disease depending on the hypothesis of genetic predisposition and molecular mimicry as factors contributing to the advancement of AIH. The mechanisms by which medicines perhaps initiate AIH involve the secretion of medication metabolites that bind to proteins and act as antigenic complexes stimulating the generation of autoantibodies, principally CYP1A2 and CYP2A6, and the sensitization of lymphocytes. Weiler-Normann and Schramm established a categorization of DILI with autoimmune features and AIH [14, 15].

Pathophysiology

T cells targeting the self-epitope become primed and expand, which leads to induction and perpetuation of autoimmune-mediated liver damage. Molecular mimicry is well explained in AIH-2, in which the key target of humoral and cellular autoimmune responses has been defined as the liver enzyme Cytochrome P450 2D6 (CYP2D6), which is the target of the anti-LKM1 antibody. An amino acid sequence of CYP2D6 reveals an elevated level of homology with proteins encoded by HCV and members of the herpes virus family (for example, cytomegalovirus, Epstein–Barr virus, and herpes simplex virus) [16, 17]. The immune response in AIH is probably induced by the presentation of self-antigens to uncommitted naive CD4+ T helper (TH0) cells. Antigen-Presenting Cells (APCs), such as Dendritic Cells (DCs), macrophages, and B cells, are included in the processing and presentation of self-antigens to the T Cell Receptor (TCR) on TH0 cells. The liver is home to several types of specialized APCs, involving liver sinusoidal endothelial cells, Kupffer cells, and DCs; consequently, antigen presentation to both CD4+ and CD8+ effector T cells can occur locally, potentially avoiding the need for trafficking to the regional lymph nodes and, in doing so, skewing immune responses towards tolerance. CD4+ TH0 cells become activated during antigen presentation in the availability of appropriate co-stimulatory signals and undergo maturation into distinct T helper cell populations, based on the cytokine milieu to which they are exposed. TH0 lymphocytes differentiate into T Helper 1 (TH1) cells in the presence of IL-12, whereas they differentiate into T-Helper 2 (TH2) cells in the presence of IL-4 [18, 19]. Multiple physiological metabolites in macrophages have exhibited immunoregulation properties and exerted protective effects in various disease models. Itaconate, produced from citrate, is one of the most abundant metabolites in activated macrophages. It exerts protective effects on several inflammation-associated diseases by preventing excessive inflammation. Under a certain stimulus, citrate is primarily catalyzed and transformed to cis-aconitate by aconitate hydratase-2. Subsequently, cis-aconitate is transformed to itaconate by cis-aconitate decarboxylase. Additionally, 4-Octyl Itaconate (OI), a cell-permeable derivative of

itaconate, exhibits anti-inflammatory activity by activating Nuclear factor-erythroid 2-related factor 2 (Nrf2), which is a pivotal transcription factor that regulates multiple antioxidant genes such as Heme Oxygenase-1 (HO-1). It can bind with the genes that have the Antioxidant Response Element- (ARE-) like sequences in their regions and promote the elimination of Reactive Oxygen Species (ROS) to exert protective effects. It has been observed that Nrf2 protects normal cells from DNA damage by reducing ROS and protecting tumor cells against chemotherapy. Additionally, Nrf2 currently resulted to binds with the promoter regions of some proinflammatory cytokines such as Interleukin-6 (IL-6) and directly prevents their transcription to alleviate the inflammatory response. Previous studies have verified that Nrf2 activation played an indispensable function in alleviating liver damage [20].

Diagnostic Criteria

Diagnosis requires the presence of characteristic features and the exclusion of other conditions that resemble AIH. The diagnosis of AIH is depending on the presence of positive autoantibodies, increased transaminase and IgG levels, and interface hepatitis on liver biopsy [21].

Laboratory Features

Laboratory studies typically reveal elevation of Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) levels, but levels are generally <500 U/L, but on rare occasions can range between 500 U/L–1000 U/L. Some patients perhaps have elevated conjugated bilirubin and alkaline phosphatase necessitating exclusion of extrahepatic biliary obstruction, cholestatic forms of viral hepatitis, drug-induced disease, Primary Biliary Cirrhosis (PBC), and Primary Sclerosing Cholangitis (PSC). The alkaline phosphatase rarely exceeds 4 X normal and generally remains <2 times normal. Another characteristic laboratory feature of AIH is hypergammaglobulinemia, with a selective increase in IgG, which is 1.2–3.0 times higher than the upper level of normal. It should be noted that HLA typing has not been endorsed as a diagnostic or prognostic tool [22, 23].

Liver biopsy

A liver biopsy examination is crucial to establish the diagnosis and evaluate disease severity to determine the need for treatment. Serum aminotransferase and gamma-globulin levels do not predict the histologic pattern of damage or the presence or absence of cirrhosis. Liver biopsy is considered the gold standard for the assessment of liver fibrosis in AIH patients. Histologic changes, such as ductopenia or destructive cholangitis, perhaps indicate a variant syndrome of AIH and primary sclerosing cholangitis, AIH and primary biliary cirrhosis, or autoimmune cholangitis, and the findings of steatosis or iron overload perhaps suggest alternative diagnoses, such as nonalcoholic fatty liver disease, Wilson disease, chronic hepatitis C, drug toxicity, or genetic hemochromatosis [24-26]. Liver biopsy can also reveal features of biliary injury pointing towards autoimmune cholangiopathy or overlap syndromes and can also reveal features suggestive of other liver diseases [27].

Autoantibodies

A key component of the criteria developed by the IAIHG is the detection by indirect immunofluorescence of autoantibodies to constituents of the nuclei (ANA), Smooth Muscle (SMA), and Liver Kidney Microsome Type 1 (antiLKM-1). Autoantibody detection not only assists in the diagnosis but also permits differentiation of AIH in type 1 and type 2. ANA and SMA that characterize AIH type 1 and anti-LKM-1 that define AIH type 2 are practically mutually exclusive; in those rare instances when they are present simultaneously, the clinical course is identical to that of AIH type 2 [28, 29]. Anti-nuclear antibody ANA is readily detectable as nuclear staining in the kidney, stomach, and liver. On the latter in particular, the ANA pattern perhaps detected as homogeneous, or coarsely or finely speckled [30]. Smooth muscle antibody SMA is detected in the kidney, stomach, and liver, where it stains the walls of the arteries. In the stomach, it also stains the muscularis mucosa and the lamina propria. On the renal substrate, it is possible to visualize the V, G, and T patterns; V refers to vessels, G to glomeruli, and T to tubules. The V pattern is present also in non-autoimmune inflammatory liver disease, autoimmune diseases not affecting the liver, and viral infections, but the VG and VGT patterns are more specific for AIH. The VGT pattern corresponds to the so-called 'F actin' or Microfilament (MF) pattern demonstrated using cultured fibroblasts as substrate [31, 32]. Anti-liver kidney microsomal antibody Anti-LKM-1 stains brightly the liver cell cytoplasm and the P3 portion of the renal tubules but does not stain gastric parietal cells [33].

Treatment

The purpose of AIH treatment is complete biochemical and histological remission, with minimum side effects of treatment, inhibiting fibrosis progression [34]. Primary treatment consists of steroid induction therapy, where the choice is based on histological severity and the stage of fibrosis, followed by maintenance therapy with a steroid-sparing agent. The ultimate goal of treatment is to decrease long-term liver-related morbidity and mortality and to accelerate the quality of life [35]. Corticosteroid therapy is effective for all forms of AIH. Prednisone (or prednisolone) alone in combination with azathioprine provides symptoms and improves laboratory and histological manifestations of liver inflammation in most

patients. It also ameliorates or inhibits hepatic fibrosis and elevates the 20-year life expectancy to 80%. Outcomes for recent therapy can be ameliorated by early recognition and treatment of the disease, continuation of therapy until complete resolution of inflammatory activity, the institution of ancillary regimens to inhibit complications of the medication, and early identification and treatment of problematic patients [36-38]. Both regimens are identically effective and differ only in the frequency of side effects. Histologic improvement lags behind clinical and laboratory resolution by 3 months to 8 months, and therapy should be continued for at least 3 months to 6 months beyond this point of improvement. Treatment is often maintained for at least 2 years before withdrawing from drug therapy is considered. The endpoints for treatment include remission, treatment failure, incomplete response, or advancement of drug toxicity [39, 40]. Prednisone is used alone in patients with severe cytopenias, active malignancies, pregnant or considering pregnancy, and those with complete Thiopurinemethyl Transferase (TPMT) enzyme deficiency. Combination therapy is associated with fewer side effects and is preferred when treatment is anticipated to be longer than 6 months and in patients at risk of side effects involving postmenopausal women, brittle diabetics, labile hypertensive, and osteoporotic patients [41-44]. Predniso(lo) ne (0.5 mg/kg-1 mg/kg) as primary therapy followed by the addition of azathioprine after two weeks is the first-line treatment of autoimmune hepatitis [45].

Alternative treatments

Mycophenolate Mofetil (MMF) is a purine antagonist that selectively prevents the proliferation of activated lymphocytes. It has been observed to be effective in AIH patients intolerant to azathioprine. Thereupon, in patients for whom standard immunosuppression fails to induce stable remission or who are intolerant to azathioprine, MMF, together with prednisolone, is recently the treatment of choice [46, 47]. Calcineurin inhibitors, cyclosporine, and tacrolimus have been used as a rescue treatment for difficult-to-treat cases of AIH [48]. Budesonide is a corticosteroid with a very high affinity for the glucocorticoid receptor and high first-pass liver metabolism; hence, it is presently receiving considerable attention as an alternative to prednisone or prednisolone as the initial treatment of AIH [49]. Anti-TNF-a agents, such as infliximab, are commonly used to treat immune-mediated diseases such as rheumatoid arthritis, psoriasis, and IBD. There is anecdotal evidence that infliximab is efficacious in the management of difficult-to-treat cases of AIH [50].

Liver transplantation

Liver transplantation is the ultimate treatment for most patients who present with fulminant liver failure and those who reach end-stage chronic liver disease, but AIH perhaps recurs after transplantation. LT is indicated for AIH patients with acute liver failure who do not respond to immunosuppressive treatment, present with end-stage chronic liver disease, and have hepatocellular carcinoma that meets the transplant criteria. Although patients with a chronic presentation of AIH generally respond well to immunosuppressive treatment, approximately 10% will eventually require LT. Patients who do not reach remission after 4 years of therapy are the most frequent candidates for LT. The indications for LT for end-stage chronic AIH are identical to those for PBC and other end-stage liver diseases [51, 52].

Conclusion

Autoimmune Hepatitis (AIH) is a chronic inflammatory hepatopathy that can lead to end-stage liver failure and death. The only known bacterial genus associated with AIH is Rickettsia, as one of its proteins drives an autoimmune response mediated by $CD4^+$ T cells. T cells targeting the self-epitope become primed and expand, leading to the initiation and perpetuation of autoimmune-mediated liver injury. The diagnosis of AIH is depending on the presence of positive autoantibodies, elevated transaminase, and IgG levels and interface hepatitis on liver biopsy. Predniso (lo) ne (0.5 mg/kg-1 mg/kg) as primary therapy followed by the addition of azathioprine after two weeks is the first-line treatment of autoimmune hepatitis.

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Data Sources

Sources searched include Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, Scopus database, Scielo and Cochrane database. Search terms included: risk factors, pathophysiology, diagnosis and management of autoimmune hepatitis.

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