

Autoimmune Hepatitis: A Review

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Abstract

Autoimmune Hepatitis (AIH) is a periportal hepatitis with increased immunoglobulins and auto antibodies, which primarily responds to immunosuppression. It affects women 3.6 times more commonly than men. It is postulated that an environmental agent, either a drug or a virus or another agent seems to trigger a T-cell mediated cascade directed against liver antigens in genetically predisposed individuals to cause AIH.

Diagnosis requires exclusion of other causes of liver disease. The diagnostic criteria have been defined in a simplified scoring system introduced by the International Autoimmune Hepatitis Group (IAIHG) in 2008.

Current treatment of AIH is based on guidelines published by the American Association for the Study of Liver Diseases (AASLD) in 2002 and comprises of corticosteroids with azathioprine. Steroids tend to carry a high complication risk profile; hence several newer immunomodulators and biologics are in different stages of trials to assess their efficacy and safety.

Introduction

Definition and Historical Background:

The term Autoimmune Hepatitis (AIH) is used to describe a mostly chronic, but many times, acute and fulminant form of inflammatory liver disease, which can affect any age group but tends to predominate in women. The etiology remains elusive but is postulated to be related to an autoimmune process, triggered by either an environmental or intrinsic factor.^{1,2} AIH can present acutely in as many as 40% of cases.^{1,2}

This disease entity was first described in 1950 by Waldenstrom as a chronic form of Hepatitis in young women.² In 1965, it became designated by Mackay et al. as "Autoimmune Hepatitis".² Since then, it has been known by a variety of terms, including active chronic hepatitis, chronic active hepatitis or autoimmune chronic active hepatitis and by other names such as chronic aggressive hepatitis, lupoid hepatitis and plasma cell hepatitis. In 1994, the International Autoimmune Hepatitis Group designated "Autoimmune Hepatitis" as the most accurate and suitable term for the condition.^{1,2}

Classification:

The marked heterogeneity of AIH in regard to its variable presenting features, spectrum of disease severity, and presence of characteristic auto antibodies as well as response to therapy has led to several proposals for classification of the disease. Since its first description, there have been eight types of AIH proposed but as the extensive overlap of different autoantibodies in the various proposed types became clearer, their clinical significance declined. Today, Type 1 and Type 2 AIH are the only two types widely recognized.¹⁻³

Type 1 AIH is mainly characterized by circulating antibodies to nuclei (ANA), smooth muscle (SMA) and Soluble Liver Antigen/Liver Pancreas (SLA/LP).³

In 1987, a discrete form of AIH was discovered in children and young adults. It was characterized by antibodies to a particular epitope on cytochrome P450 (IID6) enzyme located in liver and kidney microsomes. Thus, a classification of AIH based on circulating autoantibodies was first proposed. This form became designated as Type 2 AIH and is associated with antibodies to liver/kidney microsomes (ALKM-1) and antibodies to liver cytosol antigen (ALC-1 or LC1).^{1,2}

Historically, Type 3 AIH represented patients with SLA antibodies or antibodies against the liver pancreas antigen (LP). Since these antibodies, designated together as SLA/LP, especially the former, are also found in patients with the classic form of AIH, these patients are now classified under Type 1 AIH.^{2,3}

Epidemiology:

AIH is a relatively uncommon disorder but according to published literature, affects women 3.6 times more commonly than men.^{1,2} It can present at any age and in any ethnic group;² however, incidence and characteristics of AIH differ in various geographic regions. Type 2 AIH seems to be more frequent in southern Europe, whereas Type 1 AIH seems to be much more common in the US and Northern Europe. AIH Type 2 seems to occur more commonly in young adults and children, but the female to male preponderance persists even in children.^{1,4}

According to a 1998 Norwegian study by Boberg and colleagues, incidence of Autoimmune Hepatitis among white Northern Europeans is around 1.9 per 100,000 with a prevalence of 16.9 per 100,000.⁴ In 1999, Milkiewicz et al⁵

reported that 2.6 percent of liver transplantations in Europe were performed in patients with AIH. Weisner and colleagues⁶ reported a liver transplantation incidence of 5.9 percent for patients with AIH in the United States. In children, 10% of patients with AIH fail to respond to medical therapy and go on to require alternative therapies or liver transplantation.⁷

Approximately 18% of patients with auto-immune liver disease present with features characteristic of a second auto-immune hepatobiliary disease, usually Primary Biliary Cirrhosis (PBC) or Primary Sclerosing Cholangitis (PSC).⁸ These are the so-called "autoimmune hepatobiliary overlap syndromes". Patients diagnosed with PBC seem to be on an average 12 years older than patients with AIH and PSC. The female preponderance is even more marked in PBC, compared to AIH. PSC does not seem to follow their pattern in this regard.⁸

Etiology and Pathogenesis

The Mechanism of Inflammatory Injury:

The most common theory of the mechanism of inflammatory injury in AIH postulates that an environmental agent, either a drug or a virus or another agent seems to trigger a T-cell mediated cascade directed against liver antigens in genetically predisposed individuals. Various mechanisms have recently been identified. The most important and convincing seems to be the model of auto reactive T-cells. It is postulated that a peripheral break of tolerance against liver-expressed antigens is sufficient to induce autoimmune liver disease, which can occur without prior liver damage.⁹

Etiologic triggering agents:

The so-called possible triggers that have been proposed include viruses, vaccines, drugs or herbs.^{10,11}

Infectious Trigger/Viruses:

Different reports in literature have implicated the viral hepatitis as potential causes. Association between AIH and Hepatitis A, Hepatitis B and Hepatitis C has been reported. AIH has also been reported to develop in association with vaccination against viral hepatitis A and B.^{10,11}

Other viruses implicated in the development of AIH or Hepatitis with autoimmune features includes human herpesvirus 6, HIV, measles virus, EBV and CMV.^{10,11}

Drugs:

Drugs that have been implicated in the development of AIH include Nitrofurantoin, the ADHD drugs Methylphenidate and Atomoxetine, Propylthiouracil, Risperidone, the anti-tuberculous agents Rifampin and Pyrazinamide, Beta Interferon, Doxycycline, (as well as Minocycline), Methyl-Dopa, Ranitidine, Oxyphenisatin,

Diclofenac, Indomethacin, Statins and Ezetimibe.^{10,11}

Imatinib, which is an immunomodulatory antineoplastic agent used in CML and gastrointestinal stromal tumours, has also been reported as potentially causing an acute form of hepatitis with autoimmune features.^{10,11}

Herbal agents:

Herbs that have been reported as potential triggers of AIH include Black cohosh, Ma Huang (Ephedra), Dai-saikoto, Sho-saikoto and melatonin.^{10,11}

Genetic Predisposition:

Two important serotypes associated with Type 1 Autoimmune Hepatitis are HLA-DR3 and HLA-DR4.¹⁰ AIH type 2 is associated with HLA DR7 and HLA-DQB.¹⁰

HLA-DR3 serotype is associated with a more severe disease pattern with an early onset and occurs in girls and young women. It also usually signifies a decreased response to corticosteroids; however extra-hepatic manifestations are less common in HLA-DR3 serotype associated AIH. HLA-DR3 serotype also occurs more commonly in caucasians.^{10,11}

HLA-DR4 serotype associated disease occurs more commonly in older adults and usually responds well to immunosuppressive therapy and exhibits more extra-hepatic manifestations.^{10,11} HLA-DR4 serotype associated disease is more common in Japan. It is also worth noting that HLA-DR4 associated disease usually occurs in patients who are not HLA-DR3 serotype

Conversely, HLA-DR2 serotype appears to be associated with a decreased incidence of AIH.¹² HLA-DRB1*0301 allele seems to have the strongest association with AIH.¹²

Polymorphism of the TNFRSF6 gene (previously known as FAS gene) at position -670 may affect the early development of cirrhosis in patients with AIH.¹³

Diagnosing Autoimmune Hepatitis

There are no pathognomonic features of the condition. Diagnosis requires careful exclusion of other causes of liver disease together with the finding of a suggestive pattern of clinical, laboratory and histologic abnormalities.¹⁴

The diagnostic criteria were last revised by the International Autoimmune Hepatitis Group in 2008 (Table-1) and a simplified scoring system was introduced to quantify the strength of the diagnosis. These criteria have a sensitivity of 88 percent and a specificity of 97 percent in diagnosing probable AIH and a sensitivity of 81 percent with specificity of 98 percent in diagnosing definite AIH. These diagnostic criteria were formulated using data from adult patients. The mean age of the

Table 1: Simplified Diagnostic Criteria for Autoimmune Hepatitis.¹⁵

Variable	Cutoff	Points
ANA or SMA	Equal to or greater than 1:40	1
ANA or SMA	Equal to or greater than 1:80	2*
Or LKM-1	Equal to or greater than 1:40	
Or SLA	Positive	
IgG	More than upper normal limit	1
	More than 1.10 times the upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	1
	Typical for AIH	2
Absence of viral hepatitis	Yes	2

Equal to or more than 6 points: probable AIH.
Equal to or more than 7 points: definite AIH.

*Addition of points achieved for all autoantibodies (maximum, 2 points).

Abbreviations: ANA Anti-neutrophil antibodies; SMA smooth muscle antibodies; Anti-LKM1 anti-liver kidney microsome antibodies 1; SLA soluble liver antigen; IgG Immunoglobulin G; AIH Autoimmune Hepatitis.

patients used by IAIHG to validate their findings was 49 years with a range of 34 to 59.¹⁵

Biochemical Markers and Autoantibodies:

The aminotransferases are typically elevated in AIH. A cholestatic picture although less common might also be present with an elevation of Alkaline Phosphatase and conjugated bilirubin. However, other hepatobiliary diseases including the autoimmune hepatobiliary overlap syndromes should be ruled out first when cholestasis is present.¹⁴⁻¹⁶ Another characteristic feature of AIH is an elevation of serum globulins, particularly IgG.^{14,15}

Main serologic markers of Autoimmune Hepatitis are circulating auto antibodies that form an important component of its classification and diagnosis.^{17,18}

Classic or Type I Autoimmune Hepatitis is mainly characterized by circulating antibodies to nuclei (ANA) and smooth muscle (SMA). Antiactin antibodies (AAA) may be more sensitive and specific than SMA in the diagnosis of AIH Type 1, but the testing is not available in most commercial laboratories. Other antibodies that seem to be associated with AIH Type I include atypical p-ANCA, anti-Mitochondrial antibodies (AMA), Anti-ds DNA, Saccharomyces cerevisiae (ASCA), a plasma-membrane sulfatide, the nuclear envelope proteins lamins A and C and a number of cytoskeleton antigens.¹⁶⁻¹⁹

Type 2 autoimmune hepatitis is associated with antibodies to liver/kidney microsomes (ALKM-1) and antibodies to a liver cytosol antigen (ALC-1 or LC1). Anti SLA/LP antibodies may also be present in children with AIH Type 2.¹⁶⁻¹⁹

Clinical Features:

AIH may present diversely. The presentation varies between asymptomatic disease to acute fulminant liver failure. Subclinical disease may also occur with eventual progression to overt symptoms of inflammatory hepatitis. The physical findings range from a normal physical examination to hepatomegaly with or without splenomegaly, to the presence of stigmata of chronic liver disease or acute decompensated cirrhosis and liver failure.^{11,14,15}

Extrahepatic manifestations of AIH may take the form of constitutional symptoms. Dermatologic and rheumatologic manifestation may occur. AIH may also present an "autoimmune hepatobiliary overlap syndromes with mixed features of AIH and PBC or PSC."^{11,14-17}

All patients suspected of AIH must be evaluated for other causes of liver injury other than PSC or PBC, as some of them may also have features with AIH.¹⁴⁻¹⁷

Histopathologic Diagnosis:

Liver biopsy findings vary from minimal non specific changes to a predominantly lymphoplasmacytic or mononuclear portal infiltrate, with the occasional presence of eosinophils, with or without fibrosis. This histological finding is considered compatible with, but not typical of AIH.^{20,21}

As disease progresses, this lymphocytic or lymphoplasmacytic infiltrate, usually associated with fibrosis, invades the sharply demarcated hepatocyte boundary surrounding the portal triad and percolates into the surrounding lobule. This periportal infiltrate is also referred to as "piecemeal necrosis" or more commonly "interface hepatitis" (Figure). Interface hepatitis is one of the three

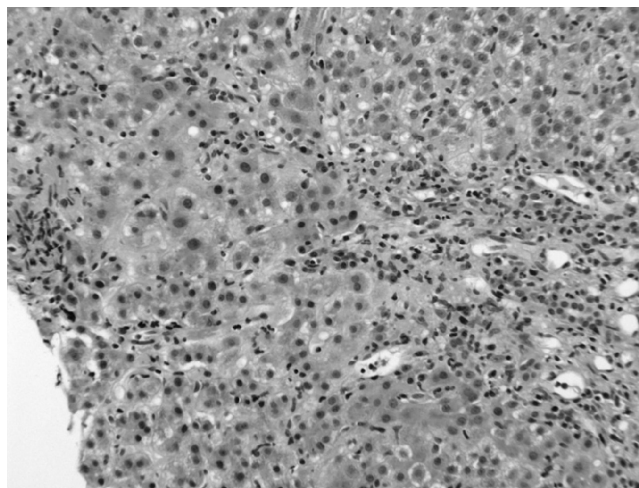


Figure:²³ This photomicrograph shows changes consistent with Interface hepatitis with plasma cell infiltration. A Hepatic Rosette is a cluster of reactive hepatocytes surrounded by inflammatory cells.

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typical features of AIH according to the 2008 diagnostic criteria.^{14,15}

Inflammatory cells actively penetrate into, and, through larger liver cells, a process called emperipolesis. Emperipolesis is also one of the three typical histologic features of AIH according to the 2008 diagnostic criteria.¹⁵

The third typical feature of AIH histology is the presence of hepatic rosettes; which are clusters of reactive hepatocytes surrounded by inflammatory cells (Figure). If there are many rosettes in a slide, the slide reveals "cobblestoning" of the hepatic parenchyma.¹⁵

All three histological features described above must be present, for a liver biopsy to be reported as having typical features of AIH.¹⁵

Histological progression of AIH results in advanced fibrosis. Moreover, at this stage, the inflammatory infiltrate connects portal and central areas, thus referred to as "bridging necrosis".^{14,20,21} Ultimately, appearance of regenerating nodules in addition to bridging necrosis, results in liver cirrhosis.^{15,21,22}

When AIH presents as an acute fulminant hepatitis, histologic diagnosis still helps in the diagnosis through the presence of plasma cell infiltrate in the portal areas which helps distinguish it from other forms of acute hepatitis. Centrilobular (zone 3) necrosis usually signifies acute disease.^{10,22}

Treatment

Though treatment guidelines have been published by the American Association for the Study of Liver Diseases (AASLD) in 2002, Autoimmune Hepatitis is really a heterogeneous disease, the treatment of which has to be individualized.¹⁴

Indications:

The absolute and relative indications that were formulated by the American Association for the Study of Liver Diseases (AASLD) in 2002 were meant to be more or less guidelines (Table-2). The decision to treat should be based on

Table-2: Indications for treatment.¹⁴

Absolute	Relative
Serum AST \geq 10-fold upper limit of normal.	Symptoms (fatigue, arthralgia, jaundice).
Serum AST 5-fold upper limit of normal and γ -globulin level \geq twice normal.	Serum AST and/or γ -globulin less than absolute criteria.
Bridging necrosis or multiacinar necrosis on histologic examination.	Interface hepatitis.

Abbreviation: AST Aspartate Aminotransferase.

a thorough review of the symptoms, the histological features on liver biopsy and the AST and gamma globulin levels. Drug-related side effects should also be a strong consideration in the choice of initial and long-term treatment strategy. Based on previously published studies, AASLD formulated absolute and relative indications of treatments with absolute indications identifying serologic and histologic findings associated with increased mortality if not treated appropriately, and relative indications being associated with increased morbidity and an overall worse prognosis.¹⁴

According to AASLD, treatment is warranted in most children at the time of diagnosis. Elderly patients have more advanced disease at presentation, but they respond well to treatment.¹⁴

Standard Regimen:

The standard regimen is Prednisone or Prednisolone with or without Azathioprine.¹⁴

Corticosteroids and Azathioprine alone or combined have yielded good results when used as maintenance regimens in both adults and children, but side effects and intolerability of both these drugs remain a major concern. There are at least three randomized controlled trials which unequivocally provide evidence for the effectiveness of steroids with azathioprine in decreasing morbidity as well as mortality. AASLD also recommended this regimen in its treatment guidelines published in 2002.¹⁴

Based on an open label trial of children with AIH published in 2006, Cyclosporine has also shown promise as first line agent as well as adjunctive agent to Prednisone and Azathioprine.²⁴

Other Therapies:

There are currently ongoing, open label as well as randomized controlled trials, in which mycophenolate mofetil (MMF), tacrolimus, as well as budesonide are being tested in order to limit the use of systemic prednisone in patients with AIH and avoid its long term side effects. These trials are also being carried out to find effective therapies for patients who are either intolerant of the standard regimen or resistant to it.²⁵⁻²⁸

Surgical Treatment:

For patients who develop End Stage Liver Disease, Decompensated Cirrhosis or severe and fulminant forms of Autoimmune Hepatitis, steroids, which are otherwise the standard of care, have little to offer and might even, worsen the prognosis.^{14,15,29} The only option for patients who are either intolerant, or resistant to all kinds of medical therapy, and those who have ESLD or decompensated cirrhosis, severe or fulminant liver failure, seems to be urgent liver transplantation. Liver Transplantation for AIH has generally

shown good long-term outcomes.³⁰

Defining Response and other Endpoints:

IAIHG published guidelines for definition of response and relapse in 1999.³¹ AASLD published guidelines to elaborate on the response to treatment in 2002 (Table-3).¹⁴

Table-3: End points of initial treatment and courses of action.¹⁴

Remission	
Definition:	Course of Action:
1. Disappearance of symptoms	Gradual withdrawal of prednisone over 6-week period
2. Normal serum bilirubin and γ -globulin levels	Discontinuation of azathioprine
3. Serum aminotransferase level normal or less than twice normal	Regular monitoring for relapse
4. Normal hepatic tissue or minimal inflammation and no interface hepatitis	
Treatment Failure	
Definition:	Course of Action:
1. Worsening clinical, laboratory, and histologic features despite compliance with therapy	Prednisone, 60mg daily, or prednisone, 30 mg daily, and azathioprine, 150mg daily, for at least one month
2. Increase of serum aminotransferase by 67 percent	Reduction of dose each month of improvement until standard maintenance levels
3. Development of jaundice, ascites, or hepatic encephalopathy	
Incomplete Response	
Definition:	Course of Action:
1. Some or no improvement in clinical, laboratory, and histologic features during therapy	Reduction in doses of medication to lowest levels possible to prevent worsening
2. Failure to achieve remission after 3 years	Indefinite treatment
3. No worsening of condition	
Drug Toxicity	
Definition:	Course of Action:
Development of intolerable cosmetic changes, symptomatic osteopenia, emotional instability, poorly controlled hypertension, brittle diabetes or progressive cytopenia	Reduction in dose or discontinuation of offending drug depending on severity of side effect Maintenance on tolerated drug in adjusted dose

According to IAIHG, complete response is defined as either or both; marked improvement of symptoms and return of serum AST or ALT; bilirubin and immunoglobulin values completely to normal within 1 year and sustained for at least a further 6 months on maintenance therapy, or a liver biopsy specimen at some time during this period showing at most minimal activity.³¹

Similarly according to IAIHG, complete response may also be defined as either or both; marked improvement of

symptoms together with at least 50 percent improvement of all liver test results during the first month of treatment, with AST or ALT levels continuing to fall to less than twice the upper normal limit within 6 months during any reductions toward maintenance therapy, or a liver biopsy within 1 year showing only minimal activity.³¹

IAIHG defines relapse as either or both; an increase in serum AST or ALT levels of greater than twice the upper normal limit or a liver biopsy showing active disease, with or without reappearance of symptoms, after a "complete" response as defined or reappearance of symptoms of sufficient severity to require increased (or reintroduction of) immunosuppression, accompanied by an increase in serum AST or ALT levels, after a "complete" response as defined above.³¹

It is noteworthy that most responders generally respond within a month of treatment.^{14,31}

It is now becoming evident that therapy should not be permanently withdrawn in any patient who has not achieved complete alleviation of all significant symptoms, complete normalization of biochemical markers as well as end of inflammation on histology. Treatment may still be tapered and finally stopped, however, in patients who continue to have minimal nonspecific portal hepatitis or inactive cirrhosis on histology.^{14,31,32}

There is no optimal duration of maintenance treatment. At least six months of maintenance treatment seems to be appropriate in most adult patients. In children, long term, low dose maintenance regimen is usually required, even though initial response is rapid.^{14,31,32}

Prognosis

According to previous prognostic studies, 40 percent of patients with untreated severe disease may die within six months of diagnosis. Cirrhosis eventually develops in 40 percent of untreated survivors.^{33,34}

Most treated patients have a good prognosis. Studies have indicated that patients, with or without cirrhosis on biopsy, generally but not always, respond to corticosteroid treatment. The 20-year survival rate for all treated patients is over 80 percent, and this rate seems to be similar to that of age- and sex-matched normal subjects from the same geographical region.^{33,34}

The response to treatment seems to be very good in children treated with corticosteroids and Azathioprine. For example, normalization of biochemical markers is seen in up to 90 percent of children after six to nine months of treatment.^{33,34}

Future Advances

Newer modalities include different immunomodulators which may be used in a more effective manner to cause

cytokine manipulation. Moreover, stem cell transplantation and transfer of T regulatory cells are also being looked at.³⁵

Conclusion

AIH is not a common condition but it is an important condition to identify in view of its poor prognosis if not recognized and appropriately treated, as well as its amenability to traditional immunosuppressive treatment.

As pointed out above, the generally agreed hypothesis as to the etiopathogenesis of AIH, points towards an environmental agent (viral infections, or drugs) as a trigger to a T cell mediated hepatocyte injury in genetically predisposed individuals. Understanding the exact pathogenesis of inflammatory injury in AIH can and will provide insights into developing new preventive and therapeutic strategies while limiting toxicity of currently used treatment.

Diagnosis requires careful exclusion of other causes of liver disease together with the finding of a suggestive pattern of clinical, laboratory and histologic abnormalities, which have been clearly defined in a simplified scoring system introduced by IAIHG in 2008.

The AASLD formulated absolute and relative indications of treatments as well as treatment guidelines in 2002 based on previously conducted clinical trials as well as expert opinion in order to come up with the best possible management plan.

There are currently ongoing open label as well as randomized controlled trials with newer immunomodulators and biologics, to assess their safety and efficacy in the treatment of patients with AIH, and minimize steroid related side effects.

As we advance into the future, we will see the treatment of autoimmune hepatitis become one with a multi-disciplinary approach.

The ultimate goal of therapy is, and will remain the improvement of quality of life of patients, and reduce the risk of end stage liver disease requiring transplantation.

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