

During the past three decades, remarkable advances have taken place in the understanding of epidemiology, natural history and pathogenesis of chronic hepatitis. Development of viral serologic treatment made Hepatologist to differentiate chronic viral hepatitis from other type of chronic liver disease including autoimmune hepatitis.

Autoimmune hepatitis is considered as chronic liver disease of unknown cause, characterized by continuing hepatocellular inflammation and necrosis, which may progress to cirrhosis.

Serum immune markers are present and the disease is often associated with other autoimmune disease. AIH cannot be explained by chronic viral infection, alcohol consumption or expose to hepatotoxic medication or chemicals.

Waldenstrom in 1950 first described a form of chronic hepatitis in young woman, and that was characterized by cirrhosis, plasma cell infiltration of liver and marked hypergammaglobulinemia.

Kunkel in 1950 and Bearn in 1956 described other features of the disease, e.g. hepatosplenomegaly, jaundice, acne, hirsutism, cushingoid facies, obesity, arthritis.

Joske in 1955 reported LE cell phenomenon in active chronic viral hepatitis.

Mackey and associates in 1956 used the term lupoid hepatitis which has no link with autoimmune hepatitis.

Histopathologic description of autoimmune hepatitis underwent several revisions.

In 1992 international panel defined the diagnostic criteria.

The term autoimmune hepatitis was selected to replace the term autoimmune liver disease and autoimmune active hepatitis.

EPIDEMIOLOGY AND NATURAL HISTORY

Annual incidence of AIH among White Northern Europeans is 1.9 per 100,000. This incidence and prevalence have remained unchanged over past two decades. AIH accounts for 6% of liver transplants in United States. AIH is a disease affecting women more than men (ratio 3:1).

Natural history of AIH is variable depends on host issues that are not clearly understood. Studies show untreated severe disease likely to die within 6 months of diagnosis.

Studies also show AIH likely to progress into cirrhosis with development of portal hypertension in significant proportion of patients (20-54%).

AIH may present as acute hepatitis, chronic hepatitis or with established cirrhosis or may present as fulminant presentation leads to hepatic encephalopathy within 4-6 hours of presentation with poor outcome unless liver transplant is obtained.

PATHOPHYSIOLOGY

Evidence suggests that liver injury in a patient with AIH is the result of a Cell- mediated immunologic attack. This human leukocyte antigen (HLA) class II on the surface of hepatocytes facilitates the presentation of normal liver cell membrane constituents to processing cells. These activated cells, in turn stimulate the clonal expansion of autoantigen-sensitized cytotoxic T lymphocytes.

Table 1: Clinical characteristics of autoimmune hepatitis

<i>Clinical features</i>	<i>Type 1</i>	<i>Type 2</i>	<i>Type 3</i>
Diagnostic autoantibodies	ASMA, ANA Antiactin	Anti- LKM P-450 IID6 Synthetic core motif Peptides 254-271	Soluble Liver-Kidney antigen Cytokeratine 8 and 18
Age	10 y - elderly	Pediatric (2-14 y) Rare in adults	Adults (30-50 y)
Women (%)	78	89	90
Concurrent immune disease (%)	41	34	58
Gamma globulin elevation	+++	+	++
Low IgA	No	Occasional	No
HLA association	B8, DR3, DR4	B14, Dr3, C4AQO	Uncertain
Steroid response	+++	++	+++
Progression to cirrhosis (%)	45	82	75

Cytotoxic T lymphocytes infiltrate liver tissue release cytokines and help to destroy liver cells.

CLINICAL FEATURES OF AUTOIMMUNE HEPATITIS (TABLE 1)

- AIH may be present as acute hepatitis, chronic hepatitis or with established cirrhosis.
- Approximately one-third of patients present with symptoms of acute hepatitis characterized by fever, hepatic tenderness and jaundice and in some patients present with chronic liver disease and other group of patients present with liver failure.
- Clinicians must consider the diagnosis of autoimmune hepatitis when confronted with a patient who has acute hepatitis or acute liver failure and for work up such patients tests include serum ANA, ASMA, serum protein electrophoresis (SPEP) and quantitative immunoglobulins and urgent liver biopsy may be transjugular route.
- Chronic hepatitis associated with AIH may range in severity from a subclinical illness without symptoms and with abnormal results in liver chemistries.
- Symptoms and physical examination findings from extra hepatic diseases associated with AIH includes:
 - Fatigue
 - Upper abdominal discomfort
 - Mild pruritus
 - Anorexia
 - Myalgia
 - Diarrhea
 - Cushingoid features
 - Arthralgias
 - Skin rashes
 - Edema
 - Hirsutism
 - Amenorrhea
 - Chest pain from pruritus
- Many patients have histologic evidence of cirrhosis at the onset of symptoms.
- About 20% patients present initially with signs of decompensated cirrhosis. Other patients of chronic hepatitis progress with unsuccessful immunosuppressive therapy. Cirrhotic patients may present with variceal bleeding, ascitis, hepatic encephalopathy may require liver transplantation.

DISEASE ASSOCIATION

AIH especially type II is associated with variety of other disorder.

- Hematologic Complications:
 - Hematologic manifestations of hypersplenism
 - Autoimmune hemolytic anemia
 - Coombs- positive hemolytic anemia
 - Pernicious anemia
 - ITP
 - Eosinophilia
- Gastrointestinal Complications:
 - Inflammatory bowel disease (6%)
 - Celiac disease
- Proliferative glomerulonephritis
- Fibrosing alveolitis
- Pericarditis and myocarditis

- Endocrine Complications:
 - Graves disease and autoimmune thyroiditis
 - Juvenile diabetes mellitus
- Rheumatologic Complications:
 - Rheumatoid arthritis and Felty syndrome
 - Sjögren syndrome
 - Systemic sclerosis
- Mixed connective tissue disease
- Erythema nodosum
- Lichen planus
- Hepatitis C connection:

Hep C (HCV) has several associations with AIH. The prevalence rate of HCV infection in patients with AIH is similar to that of general population. This indicate HCV is not an important etiology of AIH, however patients who are seropositive LKM-1 frequently are infected with HCV.

False-positive anti-HCV by ELISA method described in setting of hypergammaglobulinemia, and false-positive reaction to HCV extended by doing HCV RNA by using PCR method.

Although AIH and HCV have similar histologic features, moderate to severe plasma cell infiltration of portal tract is more common in AIH. Portal lymphoid aggregates, steatosis and bile duct damage are more common in chronic HCV.

- Overlap Syndrome

Patients with AIH may present with features of overlap classically associated with patients of Primary Biliary Cirrhosis (PBC) and Primary Sclerosing Cholangitis (PSC).

About 7% patients with autoimmune hepatitis have a disease associated with PBC, have detectable AMA, histologic finding of liver injury and patients of autoimmune hepatitis- PBC overlap syndrome may improve with steroid.

Recent studies suggest combination of ursodiol and immunosuppressants may be advisable in patients with AIH- PBC overlap syndrome.

About 6% patients of AIH have disease associated with PSC or overlap syndrome frequently associated with Inflammatory Bowel Disease (IBD). Liver biopsy shows hepatocellular and cholestatic liver chemistries and resistant to steroid therapy but treatment with ursodiol is considered.

Autoimmune cholangitis is characterized by mixed hepatic and cholestatic liver chemistries, which shows

ANA +ve, and/or ASMA, negative AMA. AMA negative patients of these group have unpredictable response to therapy with steroid or ursodeoxycholic acid.

Cryptogenic autoimmune hepatitis is characterized by clinical picture indistinguishable from autoimmune hepatitis. Diagnosis by liver biopsy. Responsive to steroid therapy.

COMMON FINDINGS AT PHYSICAL EXAMINATION

- | | |
|------------------|-----|
| • Hepatomegaly | 83% |
| • Jaundice | 69% |
| • Splenomegaly | 32% |
| • Spider angioma | 58% |
| • Ascites | 20% |
| • Encephalopathy | 14% |

All these findings may be observed in advanced case like cirrhosis.

Autoimmune hepatitis can present acutely clinical picture mimic acute viral hepatitis due to A B C D E and also CMV, EBV, drug induced, alcohol induced hepatitis and Wilson disease. It is suggested that all patients present with acute hepatitis or acute liver failure should be tested for ANA and ASMA to rule out possibility of autoimmune hepatitis.

AIH when present as chronic hepatitis or cirrhosis the differential diagnosis includes viral hepatitis, drug induced liver disease, and alcohol induced liver disease, and also NASH, genetic hemochromatosis and alpha-1 antitrypsin deficiency.

DIAGNOSIS

The diagnosis of AIH requires presence of typical features and at the same time the exclusion of other liver condition.

An international panel has developed specific criteria for the diagnosis of AIH.

Diagnosis needs clinical features that can suggestive of AIH or conversely the lack alternative conditions that may be responsible for patients hepatitis liver disease condition that are most likely to be confused with the diagnosis of AIH, are Wilson's disease, chronic viral hepatitis (specially Hep 'C') and drug induced hepatitis.

Scoring system has been established by International Autoimmune Hepatitis study group (Table 2).

With this scoring system a patient is evaluated based on 11 biochemical, epidemiologic and clinical marker before treatment and a pretreatment score is calculated.

Table 2: Diagnosis scoring system for atypical autoimmune hepatitis in adults

Category	Factor	Score	Category	Factor	Score
Gender	Female	+2	Concurrent immune disease	Any nonhepatic disease of an immune nature	+2
Alk Phos: AST (or ALT) ratio	> 3	-2	Other auto-antibodies	Anti-SLA/LP, actin, LCI, pANCA	+2
Gamma globulin or IgG (times upper limit of normal)	> 2.0	+3	Histologic features	Interface hepatitis	+3
	1.5-2.0	+2		Plasma cells	+1
	1.0-1.5	+1		Rosettes	+1
	< 1.0	0		None of above	-5
ANA, SMA, or anti-LKMI titers	> 1:80	+3	HLA	Biliary changes	-3
	1:80	+2		Atypical features	-3
	1:40	+1		DR3 or DR4	+1
	< 1:40	0			
AMA	Positive	-4	Treatment response	Remission alone	+2
				Remission with relapse	+3
Viral markers of active infection	Positive	-3	Pretreatment score		> 15
	Negative	+3	Definite diagnosis		
Hepatotoxic	Yes	-4	Probable diagnosis		10-15
	No	+1	Post- treatment score		
Alcohol	< 25 g/day	+2	Definite diagnosis		> 7
	> 60 g/day	-2	Probable diagnosis		12-17

Score greater than 15 prior to corticosteroid are consistent with “definitive” diagnosis of AIH. A definite diagnosis after corticosteroid treatment requires a score greater than 17 and alternatively a score less than 10, are unlikely to a case of AIH.

At the present time, an important use of the scoring system is to exclude AIH in patients who have documented hepatitis C.

The liver biopsy remains essential to the diagnosis of and evaluation of and disease severity in patients with AIH.

Histologic examination is also critical for diagnosing varying syndromes of AIH, e.g. overlap syndrome like AIH and primary sclerosing cholangitis, AIH and primary biliary cirrhosis or AIH and autoimmune cholangitis.

TREATMENT

Diagnosis of AIH does not mandate therapy in every case. Like other chronic liver disease the decision to treat represents a careful balance between the benefit and risk of therapies and knowledge of natural history of AIH help in predicting which patient may progress to end stage liver disease and thus benefit from treatment.

Steroid based treatment regimes are the mainstay of therapy and successful in causing a clinical, biochemical and histological remission in majority of patients.

But randomized controlled trials showed that combination of prednisone and azathioprine enhanced survival, improved symptoms and laboratory tests and majority patients improved histological findings, these controlled trials done in patient with Type I AIH, but others suggest Type II and Type III benefit from immunosuppressive therapy.

A panel of experts has given guidelines for indication of treatment (Table 3).

The practice guidelines suggest that presence of interface hepatitis without bridging necrosis or multiacinar necrosis or histologic examination does not necessarily compel treatment.

Patients with compensated cirrhosis but with inflammation on liver biopsy still may benefit from short term (3-6 months) treatment trail. It is unlikely that established fibrosis or cirrhosis resolve completely with treatment, under such situation treatment may delay or obviate liver transplantation.

But with decompensate liver disease due to AIH should not be treated with steroids better should be considered for orthotopic liver transplantation.

Table 3: Indications for treatment

<i>Absolute</i>	<i>Relative</i>
Serum AST>10-fold upper limit of normal	Symptoms (fatigue, arthralgias, jaundice)
Serum AST>5-fold upper limit of normal and gamma globulin > twice normal	Serum AST and/or gamma globulin less than absolute criteria
Bridging necrosis or multiacinar necrosis on histologic examination	Interface hepatitis

Table 4: Suggested doses for initial treatment of Type I autoimmune hepatitis

<i>Time</i>	<i>Steroid alone</i>	<i>Combination therapy</i>	
	<i>Prednisone</i>	<i>Prednisone</i>	<i>Azathioprine</i>
Week 1	60	30	50
Week 2	40	20	50
Week 3	30	15	50
Week 4	30	10	50
Until clinical end point reached	20	10	50

AASLD-guidelines suggest 2 potential initial treatments, regimes for adults and for children (Tables 4 and 5).

TREATMENT END-POINTS

- Complete remission is indicated by absence of symptoms serum AST level less than 2 times of normal and histologic improvement.
- Treatment failure is defined as deterioration in patients condition during therapy.
- Incomplete patients response is defined as an improvement that is insufficient to satisfy remission criteria.
- Drug toxicity may occur.
- Patients with severe disease have high short-term mortality rate if they show normalization of at least one laboratory parameter.

- Histological remission tends to lag behind clinical and lab. Remission by 3-6 months. Follow up liver biopsies can optimize histologic remission.

TREATMENT END-POINTS AND DURATION OF THERAPY

It has been clear that immunosuppressive therapy improves AIH, either prednisolone alone or in combination with Azathioprine, induces clinical, biochemical and histological remission in 65% patients.

Ten years life expectancy for treated patients with or without cirrhosis at presentation.

No firm guideline regarding duration of therapy are available. However, relatively long course of immunosuppressive therapy are needed in severe cases.

TREATMENT FAILURE

Nine percent of patients experience treatment failure with standard therapy. Prednisolone (60 mg/d) alone or prednisolone (30 mg/d) plus Azathioprine (150 mg/d). Patients who are resistant to steroid can be treated with cyclosporine or tacrolimus.

RELAPSE

Relapse occurs in 50% of patients within 6 months of treatment withdrawal in 80% of patients within 3 years of treatment. Patients who relapse twice require indefinite therapy with either prednisolone or azathioprine and the dose to be filtrated, and the median dose of prednisolone require to achieve 7.5 mg/d. Some

Table 5: Treatment regimens for children

<i>Initial regimen</i>	<i>Maintenance regimen</i>
Prednisone, 2 mg/kg/d (up to 60 mg/d) For 2 weeks, either alone or in combination with Azathioprine, 1-2 mg/kg/d	a. Prednisone taper over 6-8 weeks to 0.1-0.2 mg/kg daily or 5 mg daily b. Azathioprine at constant dose if added initially c. Continue daily prednisone dose with or without Azathioprine or switch to alternate day prednisone dose adjusted to response with or without Azathioprine

authors also advocate indefinite treatment with azathioprine only.

ADVERSE EFFECTS

Cushingoid features, acne, hirsutism develop in 80% of patients after 2 years of therapy. Osteoporosis with vertebral compression, diabetes, cataract and hypertension may develop in patients treated with prolonged course.

Azathioprine can function as steroid-sparing agent and azathioprine can cause cholestatic hepatitis, nausea and pancreatitis.

LIVER TRANSPLANTATION

Liver transplantation is indicated in patients of decompensated AIH and hepatic failure secondary to AIH.

CONCLUSION

AIH is a chronic inflammatory liver disease with an unknown cause that is associated with a variety of antibodies. This immune disease affecting the liver responds well to prednisolone or a combination of prednisolone and azathioprine. The specific criteria for the diagnosis of AIH incorporate a wide range of biochemical, histological and immunologic features. With treatment majority of patients can be brought into remission though many patients require maintenance

therapy with low dose prednisolone and azathioprine. Combination therapy preferred because of lower rate of adverse effects due to corticosteroids. Not all patients need to be treated, even once diagnosis of AIH is confirmed. Drug therapy should be considered in patients with cirrhosis where biopsy demonstrates considerable inflammation. Finally some patients require orthotopic liver transplantation despite optimal medical management. Liver transplantation should be considered in patients of decompensated cirrhosis due to AIH or in severe fulminant hepatitis who fails to respond to initial therapy.

SUGGESTED READING

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