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## **AUTOIMMUNE HEPATITIS**

Autoimmune hepatitis, or autoimmune chronic hepatitis, is a progressive inflammation of the liver that has been identified by a number of different names, including **autoimmune chronic active hepatitis (CAH), idiopathic chronic active hepatitis, and lupoid hepatitis**. The reason for this inflammation is not certain, but it is associated with an abnormality of the body's immune system and is often related to the production of antibodies that can be detected by blood tests. Autoimmune hepatitis was first described in 1950 as a disease of young women and is associated with increased gamma globulin in the blood and chronic hepatitis on liver biopsy. The presence of antinuclear antibodies (ANA) and the resemblance of some symptoms to "systemic lupus erythematosus" (SLE) led to the label "lupoid hepatitis." It later became evident that this disease was not related to SLE. The disease is now called autoimmune hepatitis.

### **What are the Symptoms & how do you make the Diagnosis?**

The typical patient with autoimmune hepatitis is female (70%). The disease may start at any age, but is most common in adolescence or early adulthood. Blood tests identify ANA or smooth muscle antibodies (SMA) in the majority of patients (60%). More than 80% of affected individuals have increased gamma globulin in the blood. Some patients have other autoimmune disorders such as thyroiditis, ulcerative colitis, diabetes mellitus, vitiligo (patchy loss of skin pigmentation), or Sjogren's syndrome (a syndrome that causes dry eyes and dry mouth). Other liver diseases such as viral hepatitis, Wilson's disease, hemochromatosis, and alpha-1-antitrypsin deficiency should be excluded by appropriate blood tests, and the possibility of drug-induced hepatitis is ruled out by careful questioning.

The most common symptoms of autoimmune hepatitis are fatigue, abdominal discomfort, aching joints, itching, jaundice, enlarged liver, and spider angiomas (blood vessels) on the skin. Patients may also have complications of more advanced chronic hepatitis with cirrhosis, such as ascites (abdominal fluid) or mental confusion called encephalopathy. A liver biopsy is important to confirm the diagnosis and provide a prognosis. Liver biopsy may show mild autoimmune hepatitis, more advanced chronic hepatitis with scarring (fibrosis), or fully developed cirrhosis. Autoimmune hepatitis is characterized by a chronic inflammatory cell infiltrate. Plasma cells are the prominent cell type. Biopsies may show evidence for interface hepatitis (ie, piecemeal necrosis), bridging necrosis, and fibrosis. Lobular collapse, best identified by reticulin staining, is a common finding.

Interface hepatitis does not predict a progressive disease course. By contrast, a strong likelihood exists that cirrhosis will develop when bridging necrosis is present. The presence or absence of cirrhosis on liver biopsy is an important determinant of the patient's prognosis.

**Clinical Characteristics of Autoimmune Hepatitis:**

Clinical Features	Type 1	Type 2	Type 3
Diagnostic autoantibodies	ASMA ANA Antiactin	Anti-LKM P-450 IID6 Synthetic core motif peptides 254-271	Soluble liver-kidney antigen Cytokeratins 8 and 18
Age	Bimodal (10-20 y and 45-70 y)	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

**What conditions is it associated with?**

- **The hepatitis C connection**

- The hepatitis C virus (HCV) has several important associations with autoimmune hepatitis. The prevalence rate of HCV infection in patients with autoimmune hepatitis is similar to that in the general population. This implies that HCV is not an important factor in the etiology of autoimmune hepatitis; however, patients who are seropositive for anti-LKM-1 frequently are infected with HCV. These patients have predominant features of chronic viral hepatitis and frequently lack antibodies to P-450 IID6. Such patients respond to treatment with interferon. They should be distinguished from anti-LKM-1-positive patients who have a positive

anti-P-450 IID6, are seronegative for anti-HCV, and are responsive to steroid therapy.

- False-positive results on anti-HCV enzyme-linked immunoassay (ELISA) tests are described in the setting of hypergammaglobulinemia, including that observed in patients with autoimmune hepatitis. In patients with ANA and/or ASMA seropositivity and a positive anti-HCV, a false-positive reaction to HCV should be excluded by performing a test for HCV RNA using the polymerase chain reaction (PCR). In general, patients with definite autoimmune hepatitis have median serum titers of ASMA and ANA of 1:160 and 1:320, respectively. In contrast, these titers may be in the range of 1:80 or less in patients with true chronic viral hepatitis.
- Although autoimmune hepatitis and chronic HCV have similar histologic features, moderate-to-severe plasma cell infiltration of the portal tracts is more common in patients with autoimmune hepatitis. Portal lymphoid aggregates, steatosis, and bile duct damage are more common in patients with chronic HCV.
- **Overlap syndromes:** Patients with autoimmune hepatitis may present with features that overlap those classically associated with patients with PBC and PSC. Patients with disease that overlaps with PBC may have detectable AMA (usually in low titer), histologic findings of bile duct injury and/or destruction, and the presence of hepatic copper. These patients may improve with steroid therapy. Patients with disease that overlaps with PSC usually have concurrent inflammatory bowel disease, and the liver biopsy findings reveal bile duct injury. Findings from cholangiograms are abnormal. Such patients usually have mixed hepatocellular and cholestatic liver chemistries and typically are resistant to steroid therapy.
- **Autoimmune cholangitis** is characterized by mixed hepatic and cholestatic liver chemistries, positive ANA and/or ASMA, negative AMA, antibodies to carbonic anhydrase, and histology that resembles PBC. Patients may have an unpredictable response to therapy with steroids or ursodeoxycholic acid.
- **Cryptogenic autoimmune hepatitis** is characterized by a clinical picture that is indistinguishable from autoimmune hepatitis. ANA, ASMA, and anti-LKM-1 are negative at disease onset and may appear late in the disease course, as might anti-SLA. The disease usually is responsive to steroid therapy.

### Pathophysiology

Evidence suggests that liver injury in a patient with autoimmune hepatitis is the result of a cell-mediated immunologic attack. This attack is directed against genetically predisposed hepatocytes. Aberrant display of human leukocyte antigen (HLA) class II on the surface of hepatocytes facilitates the presentation of normal liver cell membrane constituents to antigen-processing cells. These activated cells, in turn, stimulate the clonal

expansion of autoantigen-sensitized cytotoxic T lymphocytes. Cytotoxic T lymphocytes infiltrate liver tissue, release cytokines, and help to destroy liver cells.

The reasons for the aberrant HLA display are unclear. It may be initiated or triggered by genetic factors, viral infections (eg, acute hepatitis A or B, Epstein-Barr virus infection), and chemical agents (eg, interferon, melatonin, alpha methyl dopa, oxyphenisatin, nitrofurantoin, tienilic acid). The asialoglycoprotein receptor and the cytochrome mono-oxygenase P-450 IID6 are proposed as the triggering autoantigens.

Some patients appear to be genetically susceptible to developing autoimmune hepatitis. This condition is associated with the complement allele C4AQO and with the HLA haplotypes B8, B14, DR3, DR4, and Dw3. *C4A* gene deletions are associated with the development of autoimmune hepatitis in younger patients. HLA DR3-positive patients are more likely than other patients to have aggressive disease, which is less responsive to medical therapy; these patients are younger than other patients at the time of their initial presentation. HLA DR4-positive patients are more likely to develop extrahepatic manifestations of their disease.

### **How is Autoimmune Hepatitis Treated?**

For more than 3 decades, prednisone and azathioprine have been the mainstays of drug therapy for patients with autoimmune hepatitis. Considerable variation in practice style exists when answering the following common clinical questions:

- How high a dose of prednisone should be used when initiating therapy?
- When should azathioprine be added to the patient's treatment regimen?
- When should a reduction in steroid dosing be considered?
- How long should treatment continue beyond a patient's biochemical remission?
- Should liver biopsy be performed in order to document histologic remission, prior to attempting to withdraw immunosuppression?
- Should patients receive life-long low-dose maintenance therapy with azathioprine?

Approximately 65% of patients respond to initial therapy and enter histological remission; however, 80% of these patients relapse after drug withdrawal.

Albert Czaja (1995) recently published his treatment recommendations for autoimmune hepatitis, which are as follows:

- **Absolute indications for treatment:**
  - Incapacitating symptoms
  - Relentless clinical progression
  - AST greater than 10 times the reference range
  - AST greater than 5 times the reference range and IgG greater than 2 times the reference range
  - Bridging necrosis on histology

- Multilobular necrosis on histology
- **Relative indications for treatment:**
  - Mild or no symptoms
  - AST 3-9 times the reference range
  - AST greater than 5 times the reference range and IgG less than 2 times the reference range
  - Periportal hepatitis on histology
- **No indication for treatment:**
  - No symptoms
  - Previous intolerance to prednisone or azathioprine
  - AST less than 3 times the reference range
  - Severe cytopenia
  - Inactive cirrhosis or mild portal hepatitis on histology
  - Decompensated cirrhosis with variceal bleeding
- **Czaja's guidelines for single-drug therapy are as follows:**
  - Prednisone - 60 mg/d for 1 week, 40 mg/d for 1 week, 30 mg/d for 2 weeks, and 20 mg/d until reaching the treatment end point
  - Recommendations for combination drug therapy - Prednisone 30 mg/d for 1 week, 20 mg/d for 1 week, 15 mg/d for 2 weeks, and 10 mg/d until reaching the treatment endpoint with azathioprine 50 mg/d until reaching the treatment end point
- **Treatment endpoints:** Patients may achieve 1 of 4 treatment endpoints.
  - Complete remission is indicated by the absence of symptoms, a serum AST level less than 2 times the reference range, and histologic improvement to normal or minimal activity.
  - Treatment failure is defined as a deterioration in patient condition during therapy.
  - An incomplete patient response is defined as an improvement that is insufficient to satisfy remission criteria.
  - Drug toxicity may occur.
  - Patients with severe disease have a high short-term mortality rate if they fail to show normalization of at least 1 laboratory parameter or if pretreatment hyperbilirubinemia fails to improve during a 2-week treatment trial. In contrast, patients who improve by these parameters have an excellent immediate survival rate, and their treatment should be continued.
  - Histologic remission tends to lag behind clinical and laboratory remission by 3-6 months. Follow-up liver biopsies can optimize management by avoiding medication withdrawal in patients who are not yet in histologic remission.
- **Treatment results**
  - Prednisone, alone or in combination with azathioprine, induces clinical, biochemical, and histologic remission in 65% of patients within 3 years.

The average treatment interval until remission is 22 months. The fact that therapy improves survival rates is clear. The 10-year life expectancies for treated patients with and without cirrhosis at presentation are 89% and 90%, respectively.

- Patients with a histologic diagnosis of cirrhosis still may respond well to therapy and should be offered treatment in an attempt to slow disease progression.

- **Treatment failures and incomplete responses**

- Nine percent of patients experience treatment failure with standard therapy. Treatment with high-dose prednisone (60 mg/d) alone or prednisone (30 mg/d) plus azathioprine (150 mg/d) is an alternative approach to therapy. Patients who are resistant to steroids can be treated with cyclosporine or tacrolimus.
- Thirteen percent of patients improve with standard therapy but do not achieve remission criteria. A low-dose, long-term prednisone schedule, similar to that used after relapse (10 mg/d), is reasonable. The goal of therapy is to control disease activity on the lowest dose of medication possible. Azathioprine may help to serve as a steroid-sparing agent.
- Patients should be referred for consideration of liver transplantation if they manifest signs of hepatic decompensation (eg, new onset of hypoalbuminemia or ascites).

- **Relapse**

- Relapse occurs in 50% of patients within 6 months of treatment withdrawal and in 80% of patients within 3 years of treatment. Reinstitution of the original treatment regimen usually induces another remission; however, relapse commonly recurs after a second attempt at terminating therapy. The major consequence of relapse and re-treatment is the development of drug-related complications, which occurs in 70% of patients.
- Patients who relapse twice require indefinite therapy with either prednisone or azathioprine. The dose is titrated as low as possible in order to prevent symptoms and to maintain AST 5-fold below the reference range. The median dose of prednisone required to achieve this is 7.5 mg/d. Recently, long-term therapy with azathioprine at a dose of 2 mg/kg/d was effective at maintaining remission in patients.

- **Treatment adverse effects**

- Cushingoid features, acne, and hirsutism develop in 80% of patients after 2 years of treatment, irrespective of the treatment regimen. Osteoporosis with vertebral compression, diabetes, cataracts, severe emotional lability, and hypertension may develop in patients who are treated with prolonged courses of high-dose prednisone. Premature treatment withdrawal is justified in patients who develop intolerable obesity, cosmetic changes, or osteoporosis.

- Azathioprine can function as a steroid-sparing agent. The authors have had great success and minimal drug-related adverse effects using long-term therapy with prednisone 10 mg/d plus azathioprine 50 mg/d. Patients should be co-treated with calcium and vitamin D in order to prevent the development of steroid-induced osteoporosis. Regular exercise should be encouraged. Bone densitometry performed every 1-2 years should be used to monitor patients. Signs of early osteoporosis may warrant the institution of treatment with alendronate.
- Azathioprine therapy can be complicated by cholestatic hepatotoxicity, nausea, vomiting, rash, cytopenia, and pancreatitis. These complications occur in fewer than 10% of patients treated with azathioprine at 50 mg/d.
- Teratogenicity has been ascribed to treatment with azathioprine; however, the gastroenterology literature is replete with references that describe the safe use of azathioprine and 6-mercaptopurine in pregnant women with inflammatory bowel disease. Whether this observation can be extended to pregnant women with autoimmune hepatitis and whether azathioprine can be employed safely in these patients is unclear.
- Hematologic malignancy has been reported in patients undergoing treatment with azathioprine; however, the risk of malignancy is thought to be low in patients with autoimmune hepatitis who are treated with low doses of the drug.

### **Surgical Care:**

- Liver transplantation
  - This procedure is an effective form of therapy for patients with decompensated cirrhosis caused by autoimmune hepatitis. This procedure also may be used to rescue patients who present with fulminant hepatic failure secondary to autoimmune hepatitis.
  - The long-term outlook after liver transplantation is excellent, with 5-year survival rates reported at 90% or more. Positive autoantibodies and hypergammaglobulinemia tend to disappear within 2 years of transplantation.
  - Recurrence of autoimmune hepatitis is uncommon after liver transplantation. It has been reported primarily in inadequately immunosuppressed patients and HLA DR3-positive recipients of HLA DR3-negative donors.

### **Diet:**

- Patients with acute autoimmune hepatitis and symptoms of nausea and vomiting may require intravenous fluids and even total parenteral nutrition; however, most patients can tolerate a regular diet. A high caloric intake is desirable.

- Patients with cirrhosis secondary to autoimmune hepatitis may develop ascites. A low-salt diet (generally <2000 mg of sodium per d) is mandatory in these individuals. Patients should continue to consume protein (ie, >1.1 g protein per kg body weight) given the catabolic nature of the disease and patients' high risk for developing muscle wasting.

**Activity:** Most patients do not need hospitalization, although this may be required for clinically severe illness. Forced and prolonged bed rest is unnecessary, but patients may feel better with restricted physical activity.

### **Mortality/Morbidity**

Without treatment, nearly 50% of patients with severe autoimmune hepatitis die in approximately 5 years.