

## Autoimmune hepatitis in Pakistan

Nasir Hassan Luck, Abbas Ali Tasneem

Autoimmune hepatitis (AIH) is a potentially treatable chronic liver disease (CLD) of unknown cause, characterized by ongoing hepatocellular necroinflammation which may progress to cirrhosis if untreated. AIH is a unique clinical entity, which cannot be explained solely on the basis of chronic viral infection model, alcohol consumption, or exposure to hepatotoxic medications and chemicals contact. Clinicians should consider the diagnosis of AIH in any patient who has presented with acute and chronic hepatitis with or without liver failure.<sup>1</sup> In 1950, Waldenstrom first described a type of chronic hepatitis in young women. This condition was characterized by cirrhosis, plasma cell permeation of the liver, and hypergammaglobulinaemia.<sup>2</sup>

The prevalence of AIH varies widely among different demographics. It varies from 11.6 to 16.9 cases per 100,000 persons in Europe while in Japan it is only 0.08-0.015 cases per 100,000 persons. There is no population based data on the incidence or prevalence of AIH in Pakistan. AIH is the primary indication of liver transplantation in 3% of cases in Europe. There are two main types of AIH, i.e., type I and type II based on different autoantibodies. Type 1 AIH can affect patients of any age and gender. Type 2 AIH is less common, primarily affecting girls and young women. The proportion of incidence of AIH 1 to AIH 2 is 1.5-2:1 in Europe and 6-7:1 in North America, South America, and Japan. AIH 2 is more frequently described in southern Europe than in northern Europe, United States and Japan. The genetic predisposition to AIH is quite diverse among ethnic groups worldwide. Whites of northern European ancestry have high frequency of HLA-DR3 and HLA-DR4 markers. The Japanese population has a low incidence of HLA-DR3 markers; instead they have more common association with HLA-DR4.<sup>2-4</sup>

Around 70-80% of patients are women.<sup>5</sup> AIH has a bimodal age distribution; the first peak is at age 10-20

.....  
Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation (SIUT), Karachi.

**Correspondence:** Nasir Hassan Luck. Email: nasirfcps@hotmail.com

years and a second one at age 45-70 years. The diagnosis should not be overlooked in individuals older than 70 years.<sup>6</sup> Men may be affected more commonly than women in older age groups. There are also rare forms of AIH that have features of AIH overlapping with diseases like primary sclerosing cholangitis and primary biliary cirrhosis. Many patients with AIH have no symptoms. AIH is often first detected when abnormal liver function tests are noted while investigating for unrelated reasons. Most common symptom is fatigue followed by jaundice, itching, skin rash, joint pain, abdominal discomfort, nausea, vomiting, anorexia, dark urine, and pale coloured stools. In the most advanced stage of AIH, signs and symptoms of hepatic decompensation are more obvious. The histopathologic features of AIH have been revised several times over the years. In 1992, an international panel regularized the diagnostic criteria.<sup>7</sup> The panel exempted the requirement of 6 months of disease activity to establish chronicity, and included lobular hepatitis, and re-confirmed the non-viral nature of the disease. The panel also selected incompatible histologic features, such as cholestasis, evidence of bile duct injury, and ductopenia.

For the last thirty years, corticosteroids, either alone or in combination with azathioprine, have been the foundations of drug therapy for patients with AIH.<sup>8</sup> Without treatment, approximately 50% of patients with severe AIH will die in about 5 years, and the majority of patients will die within 10 years. Treatment with corticosteroids has clearly been shown to improve the chances of survival significantly. The 10-year life expectancies for treated patients with and without cirrhosis at presentation are 89% and 90%, respectively. Substantial disparity in practice style exists when we try to answer the following frequent clinical questions:

- ◆ How high a dose of prednisone should be used at the onset of therapy?
- ◆ When should azathioprine be included to the patient's treatment regimen?
- ◆ When should decreasing the steroid dose be considered?

- ◆ How long should treatment continue after biochemical remission?
- ◆ Should liver biopsy be performed to document histologic remission, before stopping immunosuppression?
- ◆ Should patients receive life-long maintenance therapy with azathioprine?
- ◆ What is the role of other immunosuppressive agents in AIH?

Every patient diagnosed to have AIH does not require immediate treatment. The decision to treat is based upon the symptoms, laboratory parameters and severity of liver disease on histopathology. The main disadvantage of prednisone is side effects, which can include fluid retention, acne, osteoporosis, deranged blood glucose levels, risk of infections, cataract formation, high blood pressure, mood and sleep disturbances. To decrease the risks of side effects, the lowest feasible dose of prednisone is used. Azathioprine and 6-mercaptopurine can also cause side effects, including allergic reactions, leucopenia, pancreatitis, nausea, and abnormal liver function tests.

Generally imperative, treatment is continued until the disease is in remission, the treatment fails, or there are severe side effects of the treatment prescribed. Remission is defined as resolving symptoms, normalization of liver function tests, and improved liver histology. The initial period of remission usually occurs after 12 or more months of start of treatment. About 65 and 80% of patients attain remission by 18 months and three years, respectively. Certainly the life expectancy of patients in clinical remission is similar to that of the general population. Approximately 50% of patients remain in remission, once the treatment is stopped.<sup>9</sup> Nevertheless, most patients ought to restart treatment as the disease becomes active again. Relapses classically occur within the first 15 to 20 months post treatment. Relapses are more likely in those who have advanced liver fibrosis on the index liver biopsy.

Alcohol should be avoided since it can cause fatty liver and liver damage through other mechanisms. All types of alcoholic beverages can be harmful to the liver. Acetaminophen can be taken 500 mg every four to six hours, although this should not be repeated more than four times in one day.<sup>10</sup> Women who are treated for AIH can have successful pregnancies. Glucocorticoids and azathioprine are safe during pregnancy. Stopping

treatment is not recommended during pregnancy as it can lead to relapse. However, babies of women with AIH can have an increased risk of premature birth and low weight at birth. In children with AIH, 70% require treatment until adulthood. Many paediatric patients have cirrhosis at the time of diagnosis. Nearly 20 to 25% of children with AIH die and need liver transplantation as a result of progression of the disease to cirrhosis.

We have previously reported 58 cases of AIH diagnosed over 10 years from our center and determined its association with human leukocyte antigen (HLA) alleles.<sup>1</sup> The clinical profile of our patients revealed a high prevalence of cirrhosis at the time of presentation. Though most patients belonged to paediatric age group, the disease had already been very advanced. The most plausible reason for delay in the referral and diagnosis is lack of clinical suspicion of AIH as a cause of CLD. Type I AIH is more prevalent in our patients as compared to type II AIH. Also a significant number of patients with negative serology were found to have AIH on basis of typical liver histology. The role of liver biopsy, therefore, is of great importance in diagnosing this subset of patients. All the salient and characteristic features including interface hepatitis, plasma cell infiltrates, lobulitis, hepatic rosette formation along with varying degree of fibrosis were present in Pakistani patients with AIH. Histopathological evidence of cholestasis suggested predominantly advanced liver fibrosis compared to those with early stage disease. An analysis of the HLA types in our patients with AIH showed that HLA DR6 with its subtypes HLA-DRB1\*13 and HLA-DRB1\*14 were more prevalent in patients with AIH compared to controls. We also found association of HLA A2, HLA A9 (23), HLA A10 (25), HLA A19 (33), HLA B15 (63), and HLA B40 (61) with AIH. However, we could not study the HLA DQ alleles. Other finding we observed was that HLA DR 2 and DR 3 were more prevalent in the control population. Why our normal population with prevalent HLA DR 2 and DR 3 alleles does not have AIH is an open question. Perhaps dietary and environmental factors play a protective role and decrease the susceptibility and vulnerability to develop AIH.

In summary, although AIH is a rare disease, it should be considered in the differential diagnosis of CLD of unknown cause and treated aggressively to prevent progression to cirrhosis of liver.

## References

1. Hassan N, Siddiqui AR, Abbas Z, Hassan SM, Soomro GB, Mubarak M, et al. Clinical profile and HLA typing of

1. autoimmune hepatitis from Pakistan. *Hepat Mon.* 2013; 13:e13598.
  2. Waldenström J. The diagnostic importance of ACTH. *Acta Endocrinol.* 1950;5:235-42.
  3. Seki T, Kiyosawa K, Inoko H, Ota M. Association of autoimmune hepatitis with HLA-Bw54 and DR4 in Japanese patients. *Hepatology.* 1990; 12:1300-4.
  4. Boberg KM. Prevalence and epidemiology of autoimmune hepatitis. *Clin Liver Dis.* 2002;6:635-47.
  5. Czaja AJ. Special clinical challenges in autoimmune hepatitis: the elderly, males, pregnancy, mild disease, fulminant onset, and nonwhite patients. *Semin Liver Dis.* 2009;29:315-30.
  6. McFarlane IG, Heneghan MA. Autoimmunity and the female liver. *Hepatology Res.* 2004;28:171-6.
  7. Czaja AJ, Carpenter HA. Distinctive clinical phenotype and treatment outcome of type 1 autoimmune hepatitis in the elderly. *Hepatology.* 2006; 43:532-8.
  8. Johnson PJ, McFarlane IG. Meeting report: International Autoimmune Hepatitis Group. *Hepatology.* 1993; 18:998-1005.
  9. Strassburg CP, Manns MP. Treatment of autoimmune hepatitis. *Semin Liver Dis.* 2009; 29:273-85.
  10. Czaja AJ, Menon KV, Carpenter HA. Sustained remission after corticosteroid therapy for type 1 autoimmune hepatitis: a retrospective analysis. *Hepatology.* 2002; 35:890-7.
-