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Gastroenterology & Hepatology International Journal
ISSN: 2574-8009

Autoimmune Hepatitis-Profile and Response to Treatment in Indian Patients

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Research Article

Volume 4 Issue 2

Received Date: July 11, 2019

Published Date: August 07, 2019

DOI: 10.23880/ghij-16000159

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Abstract

Introduction: Autoimmune hepatitis (AIH) can have varied manifestations, commonest presentation being as chronic liver disease. The data on the disease profile in India is scanty compared to the West.

Aim: To study the clinical, biochemical, histological profile and response to treatment in patients with Auto-immune Hepatitis in Indian population.

Methods: This is a Retrospective analysis of the twenty one (12 M = 57.1%; 9 F = 42.9%) patients diagnosed with AIH according to simplified criteria for diagnosis of AIH, in the last three years (2017-2019) in the department of medical gastroenterology, Vydehi Institute of Medical Sciences, Bangalore, Karnataka, India.

Results: AIH accounted for 4.3% of all the liver diseases diagnosed during the last three years. Incidence of AIH was higher in males (12 M = 57.1%; 9 F = 42.9%; male to female ratio was 1.3:1), most common presenting symptom was jaundice, sixteen (57.1%), followed by ascites seven (33%) patients. Extra-hepatic manifestation was seen in fourteen (66.7%) patients. Eleven (52.3%) patients had cirrhosis with four (19%) patients having compensated cirrhosis, five (23.8%) patients having de-compensated cirrhosis, two (9.5%) patients presenting with features of acute on chronic liver failure, two (9.5%) patients presenting with acute hepatitis and seven (33.3%) patients presenting with features of chronic hepatitis. Nineteen (91%) patients had Type I AIH, one (4.5%) patient had Type II AIH and 1 patient had sero-negative AIH. Oral budesonide was started in 11(52%) of patients, 8(38%) were started on oral prednisolone and 2(10%) patients were started on intravenous methyl prednisolone in view of severe auto-immune hepatitis. Azathioprine was added in 19 patients and dose was modified according to the clinical response and side effects. Four (21.05%) patients developed drug intolerance, out of which one patient had severe adverse effect in the form of acute pancreatitis secondary to Azathioprine. Mycophenolate Mofetil (MMF) was given with good response. Mortality was noted in two (9.52%) patients.

Conclusion: Type I AIH was the most common type of AIH and majority of the patients presented with chronic liver disease. Majority of the patients had good resolution of the disease with Azathioprine and steroids. Therapy related complications occurred in one fifths of our patients.

Keywords: AIH-Auto Immune Hepatitis; Azathioprine; Chronic Liver Disease; Auto Antibodies.

Introduction

Autoimmune hepatitis (AIH) is a disease of unknown etiology characterized by un-resolving inflammation of the liver, the presence of interface hepatitis, hyper-gamma-globulinemia and auto-antibodies. Diagnosis is based on exclusion of common causes of chronic liver disease and by various scoring systems, supported by liver biopsy [1,2].

There is limited epidemiological data on AIH. However due to major burden of chronic viral hepatitis, AIH is considered rare in Asia [3,4]. In India few studies on AIH have been reported and prevalence is around 5% of all patients with chronic liver disease [5-11].

The majority of patients are peri- or postmenopausal females but AIH can present at any age and also affects males.Clinical manifestations of AIH vary from acute severe presentation, mild inflammatory, auto- antibody negative disease and atypical histology and overlap syndromes.Affected individuals often have concurrent extra hepatic autoimmune disorders. Although the pathogenesis is unclear, AIH is thought to have a basis in aberrant autoreactivity to hepatocytes in genetically susceptible individuals. Onset of symptoms is usually associated with non-specific symptoms such as fatigue, right upper quadrant pain and/or malaise, but a significant proportion of patients either present with an acute hepatitis, recurrent hepatitis or first time present with decompensation of chronic liver disease [3]. Sometimes they have no obvious clinical evidence of liver disease but diagnosed on evaluation of persistently deranged liver function tests.

The diagnosis of AIH is established by the revised scoring system devised by the International Autoimmune Hepatitis Group and the International Association for the Study of Liver [12,13]. The overall sensitivity of the score to establish a diagnosis of definite or probable AIH was 89.8%, however, the specificity for discriminating AIH from over- lapping syndrome such as primary sclerosing cholangitis(PSC)or primary biliary cirrhosis (PBC) was low [14].

Most patients show a characteristically rapid response to immunosuppressive therapy and the disease can usually be maintained in remission on low doses of prednisolone or on azathioprine alone [8].

Most of the available literatures on the natural history, treatment and response rates to treatment of AIH are derived from studies on patients of European Caucasoid (EC) or Japanese lineage. The condition being seen in other parts of the world, but there is very little information available about the disease in Indian subcontinent.

Aim

To study the clinical, biochemical, histological profile and response to treatment in patients with Auto-immune Hepatitis in Indian population.

Methods

This is a retrospective analysis of the twenty one (12 male = 57.1%; 9 female = 42.9%) patients diagnosed with AIH in the last three years (2017-2019) in the Department of Medical Gastroenterology, Vydehi Institute of Medical Sciences, Bangalore, Karnataka, India. Patients were diagnosed as AIH according to simplified criteria for diagnosis of auto-immune hepatitis.

Clinical profile, laboratory profile, liver histology, ultra-sound abdomen and pelvis, upper gastrointestinal endoscopy, type of therapy, biochemical response to therapy and clinical outcome after therapy were noted. The methods used for detection of antibodies are as follows: anti-nuclear antibody (ANA) and anti-smooth muscle antibody (ASMA) is byindirect immunofluorescence. Anti-liver kidney microsome (AntiLKM), antibody to soluble liver antigen (SLA), anti-mitochondrial antibody (AMA) and anti-liver cytosol (LC) antibody were by immunoblot technique.

Liver biopsy was done in all patients, histological activity was scored according to modified histology activity score and fibrosis was graded according to

modified Ishak score. Liver biopsy was evaluated by histopathologist looking for portal and periportal inflammation with specific emphasis on plasma cell infiltration, rosette formation, interface hepatitis and bile duct injury features.

Treatment response and side effects to therapy was monitored at every 3 months intervals on outpatient basis, by clinical assessment, liver function testing and drop in immunoglobulin G levels. Patients are planned for repeat liver biopsy after 2 years of complete biochemical response.

Results

Among the twenty one patients diagnosed with auto-immune hepatitis twelve (57.1%) patients were males and nine (42.9%) were females, mean age of presentation was 40 years, the youngest age at presentation was 8 years and the oldest patient in our present study was 65 years. Most of the patients seventeen (81%) were between the age group of 21-60 years. There was one male patient of AIH with his 8 year old daughter also presenting with autoimmune hepatitis. Jaundice was the most common symptom, twelve (57%) out of the 21 patients had jaundice. Five (24%) of the patients had asymptomatic persistent elevated liver enzymes. Two (10%) had only hematemesis as their presenting complaint. Ascites was present in seven (33%) patients. Extra-hepatic manifestation/diseases were seen in fourteen (66.7%), hypothyroidism was seen in five (23.8%), arthralgia in nine (42.9%), diabetes mellitus in eight (38%) of the twenty one patients, one patient had Sjogren's syndrome (Anti RO-52 antibody, Anti SSA antibody, and Anti PM-Scl antibodies positive) with features of interstitial lung disease.

All the patients had documented persistent elevated liver enzymes varying from two to five times the upper limit of normal values; three (21%) patients had cholestasis. ANA alone was positive in seven (33.33%), ASMA was positive in three (14.30%), ANA and ASMA was positive in eight (38%), ANA and Antibody to SLA was positive in one (4.8%), and ANA and AMA was positive in one (4.8%) patient. ANA, ASMA, Anti SLA, Anti LKM antibodies were negative in one (4.8%) patient. Nineteen (90.4%) patients had Serum IgG value >1.1 the upper limit, and two (9.6%) patients had serum IgG value>1 time the upper limit but less than 1.1 times the upper limit of normal.

Upper gastrointestinal endoscopy was done in all patients, twelve (57%) patients had normal endoscopy, seven (33%) patients had oesophageal varices and two (10%) patients had features of portal hypertensive gastropathy.

One patient had Hepatitis A IgM antibody positive in his first presentation and on follow up, patient had persistent elevated liver enzymes upto 10 times the upper limit of normal; hence patient was evaluated further and was found to have ANA and ASMA positive with elevated serum immunoglobulin G (IgG) level. Hepatitis B surface antigen and Antibody to Hepatitis C was negative in all the patients. Among twenty one patients fourteen (66.7%) patients were subjected to per-cutaneous liver biopsy and seven (33.3%) of the patients had features of chronic liver disease with ascites, hence these patients were subjected to trans-jugular liver biopsy. Seventeen (81%) had an modified HAI score between 5-7, one (4.5%) patient had a score of 8 and three (14.3%) patients had a score of 9. Six patients (28.6%) had modified Ishak score of 1, Four (19%) had a score of 2, eight (38.1%) had a score of 3 and three (14.3%) patients had a score of 4.Twelve (57%) patients had features typical of auto-immune hepatitis on histopathology, and nine (43%) patients had features compatible with auto-immune hepatitis. Nineteen (90%) had a score of > 7 according to simplified criteria for auto-immune hepatitis, and two (10%) patients had score of 6.Oral Budesonide was started in 11(52%) of patients, 8(38%) were started on oral prednisolone and 2(10%) patients were started on intravenous methyl prednisolone in view of severe auto-immune hepatitis. Azathioprine was started at the dose of 0.75 to 1mg/kg body weight in 19 patients and dose was modified according to the clinical response and side effects reaching a target dose of 2.5 mg/kg.

Drug intolerance was noted in four out of the nineteen patients. One patient developed acute pancreatitis secondary to Azathioprine, hence Azathioprine was stopped and patient was started on MMF at dose of 1gm/day in divided doses and dose was increased gradually upto 1.5gm/day. One patient developed bicytopenia and two patients had increased hair-fall secondary to Azathioprine, thiopurine methyl transferase (TPMT) level was normal in all three patients; hence Azathioprine dosage was reduced and treated accordingly, with which bicytopenia improved and hair-fall reduced in the patients respectively.

Two patients presented with features of acute on chronic liver failure, they were advised for liver transplantation, but both the patients refused liver transplantation and eventually succumbed to the disease.

Liver function test was monitored on every 3 months interval, after 3 months of initiation of treatment seven (35%) patients had complete normalisation of elevated liver enzyme level and thirteen (65%) patients had reduction in liver enzyme level. On completion of 6 months of therapy, eleven (61%) patients had complete normalisation and by the end of 12 months of therapy fourteen (88%) patients had complete normalisation of liver function test (Table 1).

Parameter- Results
Age (in years)- 39.81 + 15.465
Female gender-9(42.9%)
Symptom at presentation 1. Jaundice - 12 (57.10%) 2. Ascites - 7 (33.30%) 3. Pruritis - 7 (33.30%) 4. Gastro-intestinal bleeding - 6 (28.60%)
Extra-hepatic manifestations- 14 (67%) 1. Hypothyroidism- 5(23.8%) 2. Diabetes Mellitus- 8 (38.1%) 3. Arthralgia – 9(42.9%) 4. Interstitial lung disease and Sjogren's syndrome – 1(4.5%)
Type of AIH 1. Type I AIH -19(91%) 2. Type II AIH -1(4.5%) 3. Antibody negative- AIH 1(4.5%)
Mode of presentation 1. Acute hepatitis-2 (9.5%) 2. Compensated cirrhosis-4(19%) 3. De-compensated cirrhosis- 5(23.8%) 4. Acute on chronic liver failure-2(9.5%) 5. Chronic Hepatitis-7(33.3%)
Biochemical profile at presentation 1. AST (IU/ML) – 241.29 + 391.33 2. ALT (IU/ML- 273.90+ 567.90 3. Total Bilirubin(mg/dl)-5.484+6.49 4. INR-1.37+ 0.598 5. Serum IgG level(mg/dl)- 2484.76 + 723.71
Antibody positivity 1. ANA alone - 7 (33.33%) 2. ANA+ASMA – 8 (38%) 3. ASMA alone - 3 (14.30%) 4. ANA+ SLA – 1 (04.8%) 5. ASMA+Anti-LKM1- 1 (04.8%) 6. Sero negative- 1 (04.8%)

Table 1: Demographic, clinical, biochemical profile of patients enrolled in the study.

Discussion

Autoimmune hepatitis, though considered uncommon in India and Southeast Asian countries, it has to be considered in the differential diagnosis of patients presenting with liver diseases; whether acute, chronic or with cirrhosis. More so in ladies, with insignificant alcohol intake, negative viral markers and especially in those patients without any risk factor for non-alcoholic fatty liver disease. In our study, Auto-immune hepatitis constitutes of about 4.3% of all the liver disease. In the other Indian studies, Auto-immune liver disease constituted 3.43%, 6% and 1.3% respectively [6,9,15]. In Europe the Prevalence is about 15-25cases per 100,000 [16], and the prevalence rate in Asian countries is gradually increasing [17]. In our study mean age of presentation was 39.81 + 15.46 which is similar to the other studies; however the incidence of AIH was higher in males (Male to Female ratio was 1.3:1) unlike majority of the published data where it is predominantly female preponderance.

The most common presenting symptom was jaundice sixteen (57.1%), followed by ascites,seven (33.3%) patients which are similar to the Indian data available. In our study eleven (52.3%) patients had cirrhosis with four (19%) patients having compensated cirrhosis, five (23.8%) patients having de-compensated cirrhosis, and two (9.5%) patients presenting with features of acute on chronic liver failure, in Other Indian studies cirrhosis was present in 86.3% and 71% respectively5, 15. Extra-hepatic manifestation was seen in fourteen (66.7%) patients .Among the antibodies ANA was positive in sixteen (76.2%) and ASMA was positive in 12 (57.1%) which is similar to study by Amarapurkar DN, et al. [5].

One patient presented with features of acute hepatitis with IgM antibody positive for Hepatitis A virus; on follow up, patient had persistent elevation of aminotransferases >10 times the upper limit of normal even after 6 months, hence patient was evaluated and found to be positive for ANA and ASMA, on further evaluation serum IgG was also elevated, hence liver biopsy was done and found to have features typical of AIH. AIH can be triggered or unmasked by the Hepatitis A infection, which is described by Singh G et al and Rahaman S M et al in their respective case studies [18,19]. AIH is known to have genetic inheritance, in our study AIH was seen in a gentleman who was in mid-twenties and his eight year old daughter, however HLA testing could not be done due to financial constraints of the patient. One patient with chronic liver disease was initially negative for auto antibodies and other workup for

liver disease, however patient had elevated serum IgG level, but after 6 months duration ASMA was positive.

Nineteen (91%) of patients had Type I AIH, one (4.5%) patient had Type II AIH and 1 patient had sero-negative AIH. All the patients were initiated on Steroids and nineteen patients were started on Azathioprine, Complete normalization was noted in eleven (61.1%) patients at the end of 6 months and by the end of 1 year complete normalization was noted in 14(87.5%) patients, with resolution of ascites in 4(80%) patients which is similar to the response noted in the study by Amarapurkar DN, et al. [5].

Drug intolerance was noted in four out of nineteen patients with severe adverse effect in the form of acute pancreatitis secondary to Azathioprine was noted in one patient, hence Azathioprine was stopped and started on MMF, with which patient had complete normalisation of liver function test by the end of three months, which was faster compared to others (Budesonide & Azathioprine)

Conclusion

Autoimmune Hepatitis was thought to be less prevalent in Asia, but however there is an increased incidence reported in Asian countries in the recent past, higher clinical suspicion is required to suspect and diagnose AIH. Type I AIH was the most common type of AIH and majority of the patients presented with chronic liver disease. Patients who are negative for auto-antibodies in initial presentation may develop auto-antibodies over the course of the disease; hence in a patient with high suspicion of AIH, repeating the antibody testing would help in better diagnostic yield. We observed faster resolution of aminotransferases in one of the patient who received MMF, but further randomized studies are required to analyse the benefits of MMF against Azathioprine. Majority of the patients had good resolution of the disease with Azathioprine and steroids. Therapy related complications occurred in one fifths of our patients.

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