Clinical Presentation, Treatment Outcome and Predictors of Severity in Autoimmune Hepatitis: A Retrospective, Multicenter Experience

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ABSTRACT

AIM: Autoimmune Hepatitis (AIH) is a chronic hepatitis of unknown etiology. It affects adults and children and can progress to cirrhosis. We aim to investigate the mode of presentation, predictors of severity and treatment outcome of AIH in Saudi patients.

METHODS: This is a multicenter retrospective study that involved patients diagnosed with AIH from 3 tertiary hospitals. Clinical, biochemical, radiological and histopathological data were collected and treatment outcomes were reported.

RESULTS: A total of 212 patients were included. Female: male ratio was 3:2 and the mean age was 36.2 ± 16.8 years while 50 patients (23.6%) were above age of 50. Abnormal liver function tests (LFTs) were found in (45%). Presentation was chronic in 37.7%, acute in 30.7%, with evidence of liver cirrhosis in 28.8% and with a fulminant disease in 2.8%. Antinuclear antibody (ANA) and Anti-smooth muscle antibody (ASMA) were negative in 65 (30.6%) and 74 (35%) patients respectively. Pre-treatment liver biopsies in 166 patients showed advanced fibrosis (stage 3 and 4) in 63.3%. On multivariate analysis, platelets, alanine transaminase (ALT) level and immunoglobulin G (IgG) level were predictors of fibrosis. Complete response was achieved in 74.5% while 9% had partial response and 16.5% had no response to treatment.

CONCLUSION: The majority of AIH patients had advanced fibrosis at the time of diagnosis and liver cirrhosis was found in nearly one-third of cases. IgG, ALT, and platelet were predictors of advanced fibrosis. Complete response to treatment was achieved in two-thirds of patients. Relying on autoimmune markers for diagnosis can be misleading.

Key words: AIH; Auto-antibodies; Azathioprine; Liver Cirrhosis; Steroids

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Aljumah AA, AlKhormi A, Al-Ashgar H, Alsaad K, Bzeizi K, Masri NA, Ghamdi HA, Alwan AA, Ibrahim A, Kuriry H, Albenmousa A. Clinical Presentation, Treatment Outcome and Predictors of Severity in Autoimmune Hepatitis: A Retrospective, Multicenter Experience. Journal of Gastroenterology and Hepatology Research 2016; 5(4): 2147-2151 Available from: URL: http://www.ghrnet.org/index.php/joghr/article/view/1818
Autoimmune hepatitis (AIH) is a chronic inflammatory disease of unknown etiology affecting primarily the liver. It is a common cause of chronic hepatitis, liver cirrhosis and end stage liver disease worldwide. AIH can occur at any age but often diagnosed at age of 40-60 and it affects women more than men with female to male ratio of 3-4:1[10]. The prevalence is estimated to range between 50 and 200 cases per 1 million in Western Europe and North America among the white population[2,3], while the international prevalence among patients with liver disease is between 11-20%[4,5]. In Asian and African countries, where viral hepatitis are endemic, the incidence of AIH is not precisely known, probably due to under reporting, but expected to be lower than in Caucasians. In one study from India, AIH accounted only for 1.7% of all causes of liver diseases in a cohort of 2401 patients[6]. In Saudi Arabia, although the prevalence of AIH among patients with liver disease is not known, it may be much less as compared to North America and European countries. In one study of 112 liver transplant patients, 14.3% of liver transplant indications were due to AIH[7]. The clinical presentation of AIH is variable as well as the response to immunosuppressive treatment based on studies from western world[8]. Limited number of studies has reported AIH among Saudi patients. In one series by Abdo et al., in which they included 39 patients, 26% of them were diagnosed incidentally through finding abnormal liver function tests(LFTs) and 38% had advanced fibrosis at the time of diagnosis. Seventy five percent had either complete or partial response while one-fourth considered non-responder[9]. In another study by Fallatah et al., patients were included; decompensated cirrhosis was found in 45% and response to treatment was either complete or partial in 54.8% of the patients[10]. We aim to study the clinical presentation, response to therapy, predictors of fibrosis and outcomes in patients with AIH in a multicenter setting from Riyadh, the capital of Saudi Arabia. The participating centers are tertiary care centers, with availability of large pool of patients, vast experience in the field and access to advanced investigative and therapeutic facilities including liver transplantation.

INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory disease of unknown etiology affecting primarily the liver. It is a common cause of chronic hepatitis, liver cirrhosis and end stage liver disease worldwide. AIH can occur at any age but often diagnosed at age of 40-60 and it affects women more than men with female to male ratio of 3-4:1[10]. The prevalence is estimated to range between 50 and 200 cases per 1 million in Western Europe and North America among the white population[2,3], while the international prevalence among patients with liver disease is between 11-20%[4,5]. In Asian and African countries, where viral hepatitis are endemic, the incidence of AIH is not precisely known, probably due to under reporting, but expected to be lower than in Caucasians. In one study from India, AIH accounted only for 1.7% of all causes of liver diseases in a cohort of 2401 patients[6]. In Saudi Arabia, although the prevalence of AIH among patients with liver disease is not known, it may be much less as compared to North America and European countries. In one study of 112 liver transplant patients, 14.3% of liver transplant indications were due to AIH[7]. The clinical presentation of AIH is variable as well as the response to immunosuppressive treatment based on studies from western world[8]. Limited number of studies has reported AIH among Saudi patients. In one series by Abdo et al., in which they included 39 patients, 26% of them were diagnosed incidentally through finding abnormal liver function tests(LFTs) and 38% had advanced fibrosis at the time of diagnosis. Seventy five percent had either complete or partial response while one-fourth considered non-responder[9]. In another study by Fallatah et al., patients were included; decompensated cirrhosis was found in 45% and response to treatment was either complete or partial in 54.8% of the patients[10]. We aim to study the clinical presentation, response to therapy, predictors of fibrosis and outcomes in patients with AIH in a multicenter setting from Riyadh, the capital of Saudi Arabia. The participating centers are tertiary care centers, with availability of large pool of patients, vast experience in the field and access to advanced investigative and therapeutic facilities including liver transplantation.

MATERIAL AND METHODS

Retrospective charts review of all patients who had definite or probable diagnosis of AIH between January 1996 and December 2013 from three tertiary care centers (King Abdulaziz Medical City, Prince Sultan Military Medical City and King Faisal Specialist Hospital and Research Center), all located in Riyadh, Saudi Arabia. Diagnosis was based on the detailed criteria of the International Group of Autoimmune Hepatitis[11,12]. All adult patients (14 years and above) diagnosed as AIH, regardless of acute or chronic presentation and whether cirrhotic or not were included in the review. Patients were excluded if they have indeterminate AIH and if they had organ transplantation before the diagnosis of AIH. Demographic data, medical history on first presentation, laboratory diagnostic tests, histopathological findings, radiological findings and medications prescribedtogether with LFTs and other laboratory tests on follow up visits were collected. Grade of inflammation and stage of fibrosis on liver biopsy were reported according to METAVIR scoring system[13,14]. The main outcomes in this study were the mode of presentation, the stage of fibrosis at time of diagnosis and the response to treatment. Disappearance of symptoms, normalization of LFTs [particularly alanine transaminase (ALT), aspartate transaminase (AST)] and serum total bilirubin 2-3 years after starting treatment was classified as complete response. Improvement of LFTs by more than 50% from pretreat-

Ethical approval

This study was approved by local ethics and research committees from each contributing center.

Statistical Analysis

Data were analyzed descriptively and inferentially using SPSS version 17. Categorical variables were analyzed with chi-square (χ²) and numerical variables with student’s t-test if they are normally distributed while Mann-Whitney test was used for non-parametric variables. Binary logistic regression was used to identify predictors of the major outcome.

RESULTS

A total of 212 patients were included in the study with a median follow up of 64 months (2-317 months). One Hundred twenty nine were females with female:male ratio of 3:2. The mean age was 36.2 ± 16.8 years and 50 patients (23.6%) were above 50 years of age at the time of diagnosis. Other baseline characteristics are shown in Table 1. Yellow discoloration of sclera, fatigue and abdominal pain were the most common symptoms occurring in 56.4, 36.3 and 22.2% respectively; while the most frequent findings on examination were jaundice (66.6%), ascites (23.5%) and splenomegaly (16%). Symptoms and signs were absent in almost one fifth of patients and the only clue to diagnosis was abnormal LFTs. Similarly, biochemical parameters were normal in a significant proportion of patients; total bilirubin was normal in 25.6%, alkaline phosphatase (ALP) in 28%, Albumin in 44% and international normalized ratio (INR) in 58.3%. On the other hand, about 95%, 91%, and 92% of patients had abnormal AST, ALT and gamma-glutamyl transferase (GGT) respectively. The trigger for further investigation in patients with normal ALT was high total

Table 1: Baseline characteristics of patients.

| Characteristics                  | Mean±SD | Frequency | Percentage |
|----------------------------------|---------|-----------|------------|
| Age                              | 36.2 ± 16.8 years | 10.8%     | 30.7%      |
| Gender                           |         |           |            |
| Male                             | 83      | 39.2%     |            |
| Female                           | 129     | 60.8%     |            |
| Mode of Presentation             |         |           |            |
| Chronic hepatitis without cirrhosis | 80     | 37.7%     |            |
| Acute hepatitis                  | 65      | 30.7%     |            |
| Cirrhosis                        | 61      | 28.8%     |            |
| Fulminating Hepatic Failure      | 6       | 2.8%      |            |
| Autoimmune Diseases              |         |           |            |
| Diabetes Mellitus                | 32      | 15.1%     |            |
| Thyroid Diseases                 | 23      | 10.8%     |            |

BMI 27.5 ± 6.1

SD: standard deviation; BMI: body mass index.
Table 2 The association between autoimmune markers and presence of high ALT, high total bilirubin and advanced fibrosis at the time of diagnosis.

| Test                  | Frequency of Positive Test | Odd Ratio for high ALT | P Value | Odd Ratio for high TB | P Value | Odd Ratio for advanced Fibrosis | P Value |
|-----------------------|---------------------------|------------------------|---------|-----------------------|---------|-------------------------------|---------|
| ANA                   | 62.4%                     | 0.545                  | 0.314   | 0.583                 | 0.807   | 1.680                         | 0.244   |
| ASMA                  | 63%                       | 2.129                  | 0.134   | 0.145                 | 0.720   | 1.520                         | 0.034   |
| ANA and ASMA          | 38.7%                     | 1.390                  | 0.589   | 0.758                 | 0.456   | 1.422                         | 0.358   |
| AMA                   | 11.2%                     | 0.726                  | 0.690   | 0.809                 | 0.711   | 0.684                         | 0.213   |
| IgG (1-2 times ULN)   | 56.1%                     | 1.758                  | 0.096   | 2.581                 | 0.015   | 3.482                         | 0.024   |
| IgG (>2 times ULN)    | 27.2%                     | 9.333                  |         | 5.606                 |         | 3.000                         |         |

ALT: alanine transaminase; TB: Total bilirubin; ANA: antinuclear antibody; ASMA: anti-smooth muscle antibody; AMA: Anti-mitochondrial antibody; IgG: immunoglobulin G; ULN: upper limit of normal.

Table 3 Predictors of advanced fibrosis at the time of diagnosis by univariate analysis.

| Variable       | Odd Ratio | P value |
|----------------|-----------|---------|
| Total Bilirubin| 1.033     | 0.334   |
| High ALT       | 0.243     | 0.001   |
| High AST       | 2.156     | 0.022   |
| ALP            | 1.064     | 0.836   |
| GGT            | 1.571     | 0.920   |
| INR            | 2.224     | 0.034   |
| Low Albumin    | 1.786     | 0.007   |
| High Creatinine| 0.385     | 0.379   |
| WBC            | 2.613     | 0.517   |
| Low Hemoglobin | 1.683     | 0.022   |
| Low Platelet   | 4.935     | 0.001   |

ALP: aspartate transaminase; GGT: gamma-glutamyl transferase; INR: international normalized ratio; WBC: white blood cells.

Table 4 Predictors of advanced fibrosis at the time of diagnosis by multivariate analysis.

| Variable       | Odd Ratio | 95% CI | P value |
|----------------|-----------|--------|---------|
| Age            | 1.005     | 0.978-1.033 | 0.696   |
| Gender         | 0.555     | 0.200-1.542 | 0.259   |
| High IgG       | 4.070     | 1.097-15.107| 0.036   |
| ALT            | 0.998     | 0.996-0.999 | 0.034   |
| Platelet       | 0.994     | 0.990-0.999 | 0.038   |
| Low Albumin    | 1.186     | 0.365-3.858 | 0.777   |
| High INR       | 1.360     | 0.345-5.299 | 0.657   |

IgG: immunoglobulin G; ALT: alanine transaminase; INR: international normalized ratio.

by interface hepatitis (82%). On univariate analysis, high AST, low albumin, low Hemoglobin and platelet were associated with presence of advanced fibrosis while high ALT was inversely related to stage of fibrosis (Table 3). On multivariate analysis, high serum IgG and low platelet were significantly associated with advanced fibrosis; on the other hand, advanced fibrosis was less likely in patients with high ALT (P = 0.034), (Table 4). Different doses of immunosuppressive agents (mainly steroids in the form of prednisone/prednisolone and azathioprine) were used with different timing of introducing azathioprine. Treatment was used according to discretionand experience of the treating hepatologist. Only 4.2% and 2% of patients required mycophenolate mofetil or tacrolimus respectively. The main reason for using the latter was immunosuppressive therapy was either unresponsiveness to steroid and azathioprine or to intolerance of azathioprine. Complete response was achieved in 74.5% while 9% had partial response and 16.5% had no response to treatment (Figure 1). The response could not be assessed based on transaminases level in 9% since these patients had normal baseline ALT and AST. These patients however showed clinical improvement and did not develop liver related complication. Seventeen patients (8%) died and 19 patients (9%) had liver transplantation. Decompensated cirrhosis was the cause of death in 12 patients while the rest had fulminant hepatitis.

**DISCUSSION**

This study has shown that AIH is a frequently encountered cause of chronic liver disease in Saudi Arabia. It has an insidious onset and no specific symptoms in large proportion of patients however acute and severe form of presentation can occur but less frequently. The prevalence of advanced fibrosis was very high in this cohort with almost one third of patients having cirrhosis on presentation. Our
patients had favorable response to treatment with complete or partial response in 83% of them.

Autoimmune hepatitis is a complex disease that represents a challenge in diagnosis and management due to the diversity of the clinical presentation, wide spectrum of the disease and variable response to treatment[19]. AIH can affect different age groups and although recognized by the presence of auto-antibodies and elevated immunoglobulins, these markers are absent in a significant proportion of patients that may reach 30%[19]. The quiescent course of the disease especially at early stage is another challenge since disease can progress slowly and evolve to cirrhosis without significant symptoms[19]. As shown in our cases, the only finding that provoked the investigation for AIH was asymmetric elevation of liver enzymes in 45% of the patients. Relying on classical presentation of AIH for diagnosis will lead to missing a large number of patients and thus not considered as an appropriate approach. Instead a high index of suspicion coupled to thorough assessment of patients is necessary whenever AIH is entertained in the diagnosis. The female: male ratio in our study of 3:2 is similar to what was reported by Abdo et al. and Fallatah et al.[19] and showed that AIH was more prevalent amongst Saudi females, however the female: male ratio was less than that was reported in the western world which is estimated to be 3:4:1. The peak age of incidence in this cohort was less than that described in the literature (20-40 years) and both findings may indicate a different environmental exposure or genetic predisposition in this part of the world. Majority of our patients were presented with chronic and insidious onset who were either asymptomatic or may have nonspecific symptoms of chronic illness, which was similar to most of published studies. Acute presentation was reported in 25-70% and often can be confused with acute viral, ischemic and drug induced hepatitis[19]. We found similar figure in our cohort (30.7%) nevertheless, the acuteness of symptoms did not specify accurately the onset of disease since a large proportion of these patients had significant fibrosis at the time of presentation and thus they most likely had acute on top of chronic liver disease. We did not find difference in response to treatment between acutely presented patients and those who have presented with more insidious onset. Liver cirrhosis is very prevalent in AIH (28% in this cohort) and always a predictor of poor outcome[19]. Similar figures were reported from several studies. Kim and his colleagues reported that 22.7% of their patients had liver cirrhosis at presentation in a cohort of Korean AIH patients[20]. Cirrhosis was more prevalent in AIH patients who presented with jaundice, reaching 50% in one European study[22] and 43% in our series. In contrast to AIH patients with early fibrosis who have excellent survival after treatment, liver cirrhosis increases the probability of death and need for liver transplant in patients with AIH and increase their risk of developing hepatocellular carcinoma[22]. Reversibility of fibrosis however was reported in cirrhotic and non-cirrhotic patients[22]. Immunosuppressive therapy remains the mainstay in treatment of autoimmune hepatitis. Induction by corticosteroids with or without azathioprine results in rapid improvement of transaminases in majority of patients. We treated all patients with a combination of prednisolone and azathioprine initially. Small proportions of patients were shifted to mycophenolate (4.2%) and tacrolimus (2%) due to intolerance to azathioprine or to unresponsiveness to steroid and azathioprine. Majority of AIH patients respond favorably to immunosuppression, in our cases, the response to treatment was observed in the first few weeks after treatment in most of the patients, however complete normalization of LFTs took up to 24 months. Three-fourth of our patients achieved that endpoint and remained in remission after long duration of follow up. Compliance however remains an important determinant for maintenance of remission. Our study has the advantage of being a multicenter, hence we avoided the possibility of selection bias, furthermore it has a reasonably large number of patient. However, as the nature of retrospective design, there are some limitations that include the lack of specified timing for performing the laboratory tests and the follow up between the 3 centers. This has led to exclusion of substantial number of patients from enrollment in this study. Further, It was possible that many patients were lost follow up and we were unable to document their outcome. Despite these limitations, our study highlighted the importance of AIH in this part of the world and the need for prospective studies to identify patients earlier with appropriate diagnosis, management and, therefore, better outcome.

CONCLUSION

Autoimmune hepatitis is an important cause of chronic liver disease in Saudi Arabia. The majority of patients were found to have advanced fibrosis at the time of diagnosis and/ or liver cirrhosis was found in nearly one-third of cases. High serum IgG, low (Normal) ALT and low platelet were predictors of advanced fibrosis. Liver transplantation was infrequent indication in our patients. Relying on autoimmune markers for diagnosis can be misleading in substantial number of patients with negative autoimmune markers. High index of suspicion and more comprehensive evaluation, that may include liver biopsy, is needed whenever this diagnosis is entertained. More than 90% patients were treated with standard therapy using steroid and azathioprine. Complete response to treatment was achieved in two-third of patients.

CONFLICT OF INTEREST

All authors declared no potential conflicts of interest.

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