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Impact of gender on the long-term outcome and survival of patients with autoimmune hepatitis☆

Thawab Al-Chalabi, James A. Underhill, Bernard C. Portmann, Ian G. McFarlane, Michael A. Heneghan*

Institute of Liver Studies, King's College Hospital, Denmark Hill, London SE5 9RS, UK

***Background/Aims*: Autoimmune hepatitis (AIH) predominantly affects women. Reasons for this are unclear and few series have assessed long-term outcomes of men with AIH.**

***Methods*: To evaluate the clinical course and outcomes of 51 men from a total of 238 consecutive patients with definite AIH at a single centre from 1971 to 2005. The primary outcome measure was death or liver transplantation.**

***Results*: Median age at diagnosis was 39 y in men and 49 y in women ($p = 0.0589$). HLA A1, B8 and DR3 allotypes and the HLA A1–B8–DR3 haplotype were more frequently expressed in men (63% vs. 45%, $p = 0.049$; 74% vs. 38%, $p < 0.001$; 62% vs. 44%, $p = 0.058$; and 50% vs. 23%, $p = 0.003$; respectively). There were no significant differences in clinical manifestations at presentation. Over 96% of patients demonstrated a complete initial response to treatment. A greater number of men experienced at least one relapse (71% vs. 55%, $p = 0.0591$). However, women were significantly more likely to die or require liver transplantation (Log rank test $p = 0.024$).**

***Conclusions*: Men with AIH appear to have a higher relapse rate and younger age of disease onset which may relate to increased prevalence of HLA A1–B8–DR3. Despite this, men have significantly better long-term survival and outcomes than women.**

***Keywords*: Autoimmune hepatitis; Gender; Cirrhosis; HLA; Autoimmune liver disease**

1. Introduction

Autoimmune hepatitis (AIH) is a disease of the hepatic parenchyma characterised by progressive inflammatory destruction. It is associated with a female preponderance, the presence of circulating autoantibodies, hypergammaglobulinaemia, interface hepatitis on liver biopsy, and it typically responds to immunosuppressive therapy [1].

The observed female gender bias is consistent with many other autoimmune diseases where there is likewise an increased susceptibility in women. Although the reasons behind this are unclear, it is well established that hormones and the hypothalamic–pituitary–gonadal system may modulate the immune response [2–10]. Physiological examples include amelioration of disease activity during pregnancy in patients with multiple sclerosis (MS) and rheumatoid arthritis (RA) [9,10]. In patients with AIH, amelioration of disease activity from the second trimester of pregnancy, followed by post-partum flares, has been demonstrated in two series [11,12]. In one of these series, disease exacerbation during pregnancy was also demonstrated, albeit in only 4/35 (11.4%) pregnancies [12].

Given the alteration of disease behaviour in conditions such as MS and RA under different hormonal environments, it might also be expected that disease expression and clinical outcome differ according to

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* Corresponding author. Tel.: +44 207 3464952; fax: +44 207 3463167.
E-mail address: Michael.Heneghan@kingsch.nhs.uk (M.A. Heneghan).

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gender. Indeed, male patients with MS demonstrate more severe disease with an increased rate of cerebellar involvement, higher rates of primary progressive disease and require assisted walking devices after a shorter time period than women [13]. Conversely in RA, disease activity is more severe and long-term outcome poorer in female patients although male patients are more likely to die from extra articular manifestations of the disease [14].

To date, there has been little described pertaining to the influence of gender on the course and outcome of AIH. A report by Czaja et al. [15] investigated outcomes in a large US tertiary referral centre and found no differences in clinical outcome between 144 women and 41 men with AIH, although an increased frequency of concurrent autoimmune diseases and an increased prevalence of human leucocyte antigen (HLA) DR4 in female patients compared to male patients were noted [15].

In view of the paucity of existing data regarding the influence of gender on patients with definite AIH, we have investigated factors affecting susceptibility to the disease, presentation, severity of illness and outcome between men and women who fulfilled diagnostic criteria for definite AIH in a European setting.

2. Methods

The medical records of 238 patients (51 male, 187 female) with a diagnosis of definite AIH, median International AIH Group (IAIHG) [1,16] score 22 (range 16–28), who presented between 1971 and 2005 at King's College Hospital (KCH) were examined from a prospectively obtained database. The influence of gender on presentation, clinical course, response to therapy, incidence of hepatocellular carcinoma and clinical outcome (time to either death or liver transplantation (LT)) was evaluated. Patients were excluded from the study if they scored less than 17 points post-treatment, or less than 15 points pre-treatment, using the IAIHG scoring system, or if there was evidence of an overlap syndrome based on histological and/or cholangiographic findings. Viral hepatitis was excluded in all patients and in patients who presented before 1990, retrospective testing for hepatitis C (HCV) antibodies was performed on stored sera. Other causes of liver disease, such as excess alcohol, drugs or herbal remedies, had been excluded by appropriate history and investigations. The study has been approved by the Ethical Committee of King's College Hospital NHS Trust.

Histological material was available in 227 patients. In 11 patients (2 male, 9 female) histological data were unavailable at accession either related to procedural risk, or due to an inadequate specimen being obtained or due to patient reluctance to undergo biopsy. Despite the absence of histology, all 11 scored $\geqslant$17 points, using the IAIHG scoring system [1]. Semi-quantitative histological assessment of the severity of chronic hepatitis was performed by blinded retrospective review of histological specimens by a single pathologist (BCP) according to the method of Batts & Ludwig [17] with grade of necroinflammatory activity classified as 0 = none, 1 = minimal or patchy, 2 = mild, 3 = moderate, 4 = severe and stage of fibrosis classified as 0 = none, 1 = portal only, 2 = periportal, 3 = septal, 4 = cirrhosis. The median interval between first and second liver biopsies was 2 years (range 1–14 years). Histological improvement was defined as a decrease in the grade or stage by at least one, and deterioration by an increase in the grade or stage by at least one. All patients were tested for the following: anti-nuclear (ANA), smooth muscle (SMA), mitochondrial (AMA) and liver–kidney microsomal (anti-LKM1) autoantibodies by indirect immunofluorescence on sections of rodent liver, kidney and stomach. HLA allotypes were tested in 150 patients (112 female and 38 male).

Time to diagnosis was defined as the time of initial symptom onset or discovery of abnormal liver function tests, to the formal diagnosis of AIH. Follow up began from the time of diagnosis and terminated with either the most recent outpatient appointment at King's College Hospital, or at the time of death of the patient or liver transplantation. The mode of presentation reflects the acuity of initial illness onset or symptomatology, and was defined as 'acute' if symptom onset to diagnosis was $\leqslant$ 6 months,'insidious' >6 months, and 'asymptomatic' if the diagnosis was made on the incidental finding of abnormal liver tests either during routine health screening or during investigation of a non-hepatic illness.

All AIH patients had been initially treated according to a standard protocol with prednisolone at 0.5 mg/kg/day (20–40 mg/day) and azathioprine at 1 mg/kg/day (50–100 mg/day). The steroid dose was subsequently individually tapered to the lowest required to maintain biochemical remission. In patients who sustained complete biochemical and clinical remission for at least 1 year on maintenance therapy, the azathioprine dose (in those who tolerated the drug) was increased to 2 mg/kg/day, the steroids were then gradually withdrawn and (if remission was sustained) treatment was continued with azathioprine alone, as described in a previous study from this centre.[18] Following this publication, it has not been our policy to completely withdraw immunosuppressive therapy from patients with AIH who remain in remission.

A complete response to treatment was defined according to the revised criteria of the IAIHG as either or both of the following: marked improvement of symptoms and return of serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT), bilirubin and immunoglobulin values completely to normal within 1 year and sustained for at least a further 6 months on maintenance therapy, or a liver biopsy specimen at some time during this period showing at most minimal activity; or, either or both of the following: marked improvement of symptoms together with at least 50% improvement of all liver test results during the first month of treatment, with AST or ALT levels continuing to fall to less than twice the upper limit of normal within 6 months during any reductions towards maintenance therapy, or a liver biopsy within 1 year showing only minimal activity [1]. Relapse was also defined using the IAIHG criteria as either or both of the following: an increase in serum AST or ALT levels of greater than twice the upper limit of normal or a liver biopsy showing active disease, with or without reappearance of symptoms, after a "complete" response as defined above; or reappearance of symptoms of sufficient severity to require increased (or reintroduction of) immunosuppression, accompanied by any increase in serum AST or ALT levels, after a "complete" response as defined above [1]. A partial or no response to initial therapy was defined according to the original IAIHG criteria [16]. Patients were defined as having achieved remission if they had normal serum biochemistry (globulins/IgG/AST), had no symptoms indicative of a relapse, and (where available) liver biopsies showed only minimal activity with no necrosis [18].

2.1. Statistical analysis

For quantitative data, analyses were performed using the Mann–Whitney and Kruskal–Wallis ANOVA tests for comparison of two and more than two independent groups, respectively. Differences in proportions were analysed by the Fisher's exact test when the number of subjects was <5, and the χ^2 test for 2×2 tables when the number of subjects in all cells was >5. The $r\times c$ χ^2 test was used to investigate independent categories forming r rows and c columns where appropriate. Data are expressed as medians and ranges. All analyses were performed using StatsDirect statistical software (Camcode, Ashwell, Hertfordshire, England). Univariate and multivariate analysis was calculated using a Cox proportional hazard model with SPSS software (Chicago, Illinios, United States of America). For continuous variables that reached statistical significance on univariate analysis, receiver operator curves (ROC) were constructed. Where the area under the curve was greater than 0.6, the Youden index was calculated. This located a cut off, above and below which a dichotomous variable could be defined as 1 and 0, respectively, thus converting the continuous variable into a categorical variable. Survival analysis was performed using the Kaplan–Meier method and Cox proportional hazard model.