Paper

Evaluating distinctive features for early diagnosis of primary sclerosing cholangitis overlap syndrome in adults with autoimmune hepatitis

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LIST OF ABBREVIATIONS:

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibody; AST, aspartate transaminase; ERCP, endoscopic retrograde cholangiopancreatography; GGT, γ-glutamyl transpeptidase; HAI, hepatic activity index; IAHG, international autoimmune hepatitis group; IgG, Immunoglobulin G; IgM, Immunoglobulin M; LFTs, liver function tests; MRC, magnetic resonance cholangiography; OLS, overlap syndrome; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SMA, smooth muscle antibody.

ABSTRACT

Aims: Overlap syndromes constitute a significant proportion of autoimmune liver disease. Our aim was to describe our cohort and evaluate practical methods of correctly diagnosing autoimmune hepatitis / primary sclerosing cholangitis overlap syndrome as early as possible clinically.

Methods: 118 autoimmune hepatitis patients were screened for cholestatic liver function tests. 24 patients with cholestatic liver function tests were investigated for possible primary sclerosing cholangitis by clinicopathological review and magnetic resonance cholangiography. Retrospectively, potential predictors of autoimmune hepatitis / primary sclerosing cholangitis overlap syndrome were compared with a control group.

Results: Overlap syndrome was diagnosed in twelve (50%) of 24 autoimmune hepatitis patients with recent cholestasis. The cholestatic group had a lower AST (p=0.012) and International Autoimmune Hepatitis Group (IAHG) score (p=0.102), and higher IgM (p=0.002) at disease presentation. More patients in the cholestatic group developed ulcerative colitis (p=0.138).

Conclusions: Identifying AIH / PSC overlap syndrome at diagnosis is often difficult. Certain clinical and biochemical features should alert the clinician. All patients with AIH, and biochemical cholestasis should be investigated with MRC.

Keywords: Autoimmune hepatitis; overlap; primary sclerosing cholangitis.

INTRODUCTION

Autoimmune liver disease largely comprises autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC). The understanding, definition, and treatment of autoimmune liver disease has changed since first described during the 1950s. Narrower case definitions and improved treatment have resulted from increased clinical awareness, enhanced by biochemical, serological, histological, and radiological techniques[1,2].

Since the 1980s, "overlap syndromes" (OLS) of autoimmune liver diseases have been described. OLS indicates a variant form of autoimmune liver disease with characteristics of AIH and PSC or AIH and PBC. The patient may present with features suggesting OLS, or develop them during the course of an initially "pure" autoimmune liver disease. Accurate categorisation and characterisation of overlap syndromes requires a high index of suspicion during evaluation of clinical, biochemical, immunological, histological and radiological features. Patients with OLS have a different disease course and require specific therapy. Compared to 20 years ago, overlap syndromes are more frequently diagnosed[3], and have been the subject of several recent clinical reviews[2,4,5.] Recognising OLS early offers optimum disease management to individual patients. Clearly defining OLS, rather than only utilising pure diagnostic categories of

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autoimmune liver disease, offers an opportunity to assess pathogenic mechanisms and develop treatment strategies.
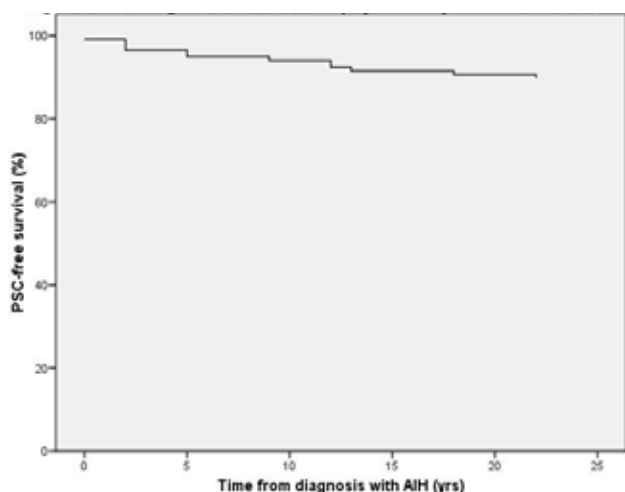

Fig 1. Time to diagnosis of AIH / PSC 'overlap' syndrome in patients with AIH. n-118

A useful tool in the study of autoimmune liver disease has been the International Autoimmune Hepatitis Group (IAHG) 'score' for AIH. This scoring for AIH was introduced in 1992 [6] and subsequently revised in 1999 [7]. The IAHG score has been validated by prospective review [8], and found to have high sensitivity (98%) and moderate specificity (60-80%) for a diagnosis of AIH [9]. These IAHG criteria have not been designed or validated for OLS. However the criteria have enabled clinicians to compare cohorts of patients, and objectively study other liver diseases for features of AIH.

In cohorts of patients with AIH, the incidence of AIH / PSC OLS is described between 7% [10] and 10% [11]. In cohorts of patients with PSC, the incidence of AIH / PSC OLS has been described as 7% [12], 8% [13], 17% [14], and 54% [15]. The variation in prevalence rates may be attributed to different patient inclusion criteria and methods of screening for disease. Study analysis reveals that some retrospective studies suffer from incomplete data, poorly defined patient groups, and variation of the criteria used for diagnosis.

The clinical importance of early diagnosis, the improved quality and availability of Magnetic Resonance Cholangiography (MRC), and the variation of disease prevalence between previously published cohorts suggest a need for further investigation,. This study seeks to define the epidemiology of AIH / PSC OLS retrospectively in a cohort of patients with AIH, and to determine which investigations should be rationally employed to improve diagnosis.

METHODS

Patient selection

118 patients attending the Liver Clinic in a large, teaching hospital with a diagnosis of autoimmune hepatitis, were included in the study. The initial diagnosis was based on clinical presentation, biochemistry, immunoglobulins and autoantibody profiles and, where a liver biopsy was performed, histology. Follow-up since initial diagnosis ranged from 2 to 26 years [median 12 years].

TABLE 1:

Clinical and laboratory characteristics at clinical presentation of AIH patients who developed cholestatic LFTs and a control AIH group

Characteristic	Cholestatic group (n=24)	Control group (n=25)	p-value
Female (%)	14 (58)	15 (60)	1.000
Age at presentation	40.2 (±15.6)	43.4 (±15.7)	0.503
AST (u/L)	271 (±338)	722 (±692)	**0.012**
ALP (u/L)	463 (±528)	263 (±180)	0.084
IgG (g/dL)	21.0 (±12.0)	20.8 (±11.5)	0.990
IgM (g/dL)	2.47 (±1.44)	1.42 (±0.78)	**0.002**
ANA or SMA (titre ≥1:40)	15	12	0.365
AMA (titre ≥1:40)	2	0	0.488
Alcohol intake <25g/day	23	22	0.600
Other autoimmune disease	1	4	0.349
Diabetes Mellitus	4	5	1.000
Ulcerative Colitis	6	2	0.138
IAHG score	8.3 (±6.0)	12.6 (±4.9)	0.102

Values are mean (±standard deviation), or categorical frequency

Study design and patient data

Those patients presumed to be at greatest risk of AIH / PSC OLS on the basis of biochemical liver function test (LFT) pattern were selected from the cohort. LFTs from the last three clinic visits were reviewed to identify all patients with cholestatic LFTs (defined as above normal ranges: GGT> 58 U/l and ALP >120 U/l). Our choice of 'cut-off' for "persistently elevated ALP or GGT" is based on previously described AIH cohorts[3]. This "cholestatic LFT group" comprised 24 patients, who subsequently underwent biliary tract evaluation by MRC, if not already performed. A radiologist (P.E.) reviewed each MRC specifically for features of PSC. Results were graded as "consistent with PSC", "suspicious of PSC", or "no evidence of PSC".

In an effort to identify distinguishing features possibly predicting OLS at the time of original diagnosis of AIH, we retrospectively compared the baseline characteristics of this cholestatic group with control patients. 25 control patients were randomly sampled from the remaining AIH cohort and matched by gender and age (±5 years). This group did not undergo evaluation by MRC.

For each patient in the study and control groups (total n=49), the IAHG score was calculated for the time of initial presentation. According to IAHG criteria[6,7], a pre-treatment aggregate score of >15 is 'definite AIH', and 10 – 15 is 'probable AIH'. Any diagnosis of ulcerative colitis was recorded, given the association with PSC.

Where available, slides from a liver biopsy performed at initial presentation i.e. before treatment, were blindly reviewed by two liver pathologists independently (M.L., M.G.) for well-described features of hepatitis or biliary disease modified from previous studies[16,17]. Depending on the variable in question, either a two-tier (0 or 1) or three-tier (0, 1 or 2) scoring system was employed. Necroinflammatory activity and fibrosis were scored according to the familiar modified Knodell hepatic activity index (HAI) system on scales of 0-4 or 0-6 [18]. For any features included in the histological component of the IAHG scoring system, the definitions used by the IAHG were followed where possible. Specifically, these describe "biliary changes" as "bile duct changes typical of PBC/PSC and/or a substantial periportal ductular reaction with copper/copper-associated protein accumulation".

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Statistical analysis

The Mann-Whitney test (for continuous, non-parametric data) was used to compare the cohort with the control group. The two-tailed Fisher's exact test (employed because of the small sample size) was used to compare categorical variables. The Gamma test for concordance or discordance of ordinal variables was used to compare each patient group for degree of histological features. p-values <0.05 were considered significant. SPSS (Chicago, IL. USA. Edition 15.0, 2007) was used for statistical analysis.

TABLE 2:

Pathological features of pre-treatment liver biopsy at diagnosis of AIH in patients who subsequently developed cholestatic LFTs compared to AIH control group

Characteristic (%)	Cholestatic group (n=10)	Control group (n=15)	p-value
Granulomatous cholangitis (%)	1 (10)	0 (0)	0.400
Lymphocytic cholangitis (%)	2 (20)	1 (7)	0.426
Neutrophilic cholangitis (%)	0 (0)	2 (13)	0.500
Concentric periductal fibrosis (%)	0 (0)	1 (7)	1.000
Ductopenia (%)	3 (30)	1 (7)	0.267
Substantial periportal ductular reaction (%)	6 (60)	6 (40)	0.124
Copper-associated protein deposits (%)	5 (50)	2 (13)	0.132
Cholate stasis (%)	2 (20)	1 (7)	0.543
Canalicular cholestasis (%)	1 (10)	5 (33)	0.289
Biliary changes (IAHG defn) (%)	4 (40)	2 (13)	0.175
Predominant lymphoplasmacytic infiltrate (%)	6 (60)	9 (60)	1.000
Liver cell rosetting (%)	2 (20)	5 (33)	0.659
Severe interface hepatitis (%)	2 (20)	6 (40)	0.232
Confluent necrosis (%)	2 (20)	7 (47)	0.439
Moderate/severe spotty necrosis (%)	3 (30)	8 (53)	0.626
Marked portal inflammation (%)	1 (10)	4 (27)	0.453
Modified HAI fibrosis staging score (mean?)	2.5 (±2.2)	1.3 (±1.3)	0.221

Values are mean (±standard deviation), or categorical frequency

RESULTS

The clinical and laboratory characteristics from the time of diagnosis of the cholestatic group of AIH patients (n=24) and the matched control AIH group (n=25) are summarised in Table 1. The cholestatic group had a lower AST (*p*=0.012), higher IgM (*p*=0.002), and lower IAHG score (*p*=0.102) at presentation compared to the control group. The other parameters recorded were similar for both groups.

Only 10 of the 24 patients with cholestatic LFTs (including four of the 12 overlap cases), and 15 of the 25 patients in the control group, had an initial liver biopsy which was available for review. Therefore statistical evaluation of histology data was limited. Of the histological features assessed (Table 2), ductopenia, substantial periportal ductular reaction, copper-associated protein deposition, and overall 'biliary changes', as defined by IAHG criteria, occurred more frequently in the cholestatic group and hepatitic features were more prominent in the control AIH group, but none of the changes reached statistical significance.

In our cohort, 12 (50%) of AIH patients with cholestatic LFTs had features of PSC on MRC. At the time of initiation of this study, eight cases of AIH had already been reclassified as AIH / PSC overlap syndrome. During the course of this study, four more patients with cholestatic LFTs were demonstrated to have cholangiographic features consistent with or suspicious of PSC.

Comparison of the AIH / PSC OLS group (defined by abnormal MRC), the cholestatic LFT group (with normal MRC), and the control AIH group, showed a similar duration of clinical follow up (mean 11.2 years, range 2-28 years). Rates of clinical remission, relapse, liver failure requiring

transplantation, or death, were similar between each of these three groups.

DISCUSSION

This study showed that, of 24 patients who were identified from a cohort of 118 AIH patients by the development of cholestatic LFTs, one half (12/24) had features of PSC on MRC evaluation, indicating a diagnosis of AIH / PSC OLS. A retrospective comparison of this cholestatic group with a control population at the time of presentation, was performed in an attempt to identify important early predictive features for developing OLS. At time of original diagnosis of AIH, patients in the cholestatic group had lower transaminases, higher serum IgM levels and a greater incidence of ulcerative colitis. IAHG scores were lower than the control group. In our cohort, no other clinical or pathological differences between the two groups were statistically significant.

Many groups have studied patients with autoimmune liver disease. Abdamlian et al.[11] prospectively studied 79 patients with a clinical diagnosis of AIH. They found that 10% had definite or probable PSC on MRC. Predictors of PSC were younger age at diagnosis, elevated alkaline phophatase at diagnosis, elevated bilirubin at time of MRC, and greater lobular activity on initial liver biopsy. Gheorghe et al.[10] studied 82 patients with AIH. Only eight of this group underwent ERCP (based on a cholestatic biochemical or histological profile), of which seven were positive for features of PSC. Therefore at least 7% of their AIH cohort had features of AIH / PSC OLS. Our finding that at least 12 (10%) of 118 AIH patients developed AIH / PSC OLS is consistent with these studies. The most comprehensive descriptive epidemiology of autoimmune liver disease prevalence and categorisation comes from Czaja et al.[15], who retrospectively reviewed 225 patients with any autoimmune liver disease. Of the 225 patients, 18% were reclassified as having OLS. 14 of 26 patients with PSC (54%) were found to have features of AIH and PSC.

Four large studies have reviewed patients with cholangiographically-proven PSC for features of AIH (assessed by IAHG criteria[7]). Kaya et al.[12] (n=211) reported 1.4% of PSC cases had 'definite' AIH and 6% had 'probable' AIH. Floriani et al.[14] (n=41) found 17% with AIH, van Burren et al.[13] (n=113) found 8% with 'definite' AIH, and Boberg et al.[4] (n=114) found 2% with 'definite' and 33% with 'probable' AIH.

The pathogenesis, time of disease onset, and sequence of progression of AIH / PSC OLS is poorly understood[5,19,20]. Retrospective analysis of the initial diagnosis is usually impossible because most patients do not have both cholangiography and liver biopsy performed at time of diagnosis of AIH. McNair et al.[21] presented five cases of AIH / PSC OLS. Two had 'pure' AIH at diagnosis, which transformed into AIH / PSC OLS subsequently. Three had concurrent features of AIH and PSC at presentation. Abdo et al.[22] reviewed 91 patients with AIH. Six patients (7%) subsequently developed cholangiographically-proven PSC. This included three patients with a previously normal cholangiogram, performed after the initial diagnosis of AIH. Gregorio et al.[23] prospectively studied children attending King's College Hospital liver clinic (London, UK) with

a diagnosis of AIH (n=28) or PSC (n=27). All patients underwent biopsy and cholangiography at presentation. Of the 27 patients with PSC, 14 (52%) had 'definite' and 13 (48%) 'probable' AIH by IAHG scores. One patient with 'pure' AIH and normal cholangiography at presentation, subsequently developed cholangiographically-proven PSC. As discussed by these and other authors, it appears that some cases of 'pure' AIH, with no features to indicate AIH / PSC OLS at diagnosis originally, subsequently can transform into AIH / PSC OLS[21,22].

The main weaknesses of this study are the small number of patients and incomplete data. Clinical notes for baseline data at diagnosis were not always available due to the long duration of follow-up. Many cases did not have a liver biopsy performed and some liver biopsies were unavailable or uninterpretable. MRC scanning is clearly preferable to ERCP from a patient perspective, but may cause claustrophobia, which prevented MRC in one case. MRC has a sensitivity of 82 to 91% and specificity of 85 to 98% [24,25], when compared to the 'gold standard' ERCP for the diagnosis of PSC. The sensitivity of MRC has improved due to better availability and quality of MR scanning. 'Small duct' PSC (biochemical and histological features of PSC, but normal cholangiography) will not necessarily have been identified by our investigations. Angulo et al.[26] identified 18 patients (5.8%) from their PSC cohort (n=309), with 'small duct' PSC. Only 25 AIH patients, out of our cohort of 118, underwent cholangiography. Therefore, the prevalence of AIH / PSC OLS may be even greater in our cohort.

This is the first study to examine whether an earlier diagnosis of AIH/PSC OLS could be made in patients with an initial clinical diagnosis of AIH. Our study reiterates the finding of other groups: a significant minority of patients diagnosed with AIH will eventually turn out to have AIH / PSC OLS. There are no clinical, biochemical, serological or histological findings which strongly predict this development. Therefore, we recommend that MRC should be performed in every case of AIH where there is an elevation of ALP and GGT, following a poor transaminase response to corticosteroids. In the event of a normal MRC, liver biopsy should be considered to look for small duct disease. The frequency with which MRC should be performed and whether MRC would reveal cases of AIH/PSC OLS in AIH patients with normal ALP and GGT remain to be determined.

The authors have no conflict of interest.

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