Original

Characteristics of Autoimmune Hepatitis in Taiwan: the 11 Years’ Experiences of a Medical Center

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Key Words
antinuclear antibody; autoimmunehepatitis

Background. Unlike in Western countries, autoimmune hepatitis (AIH) is an infrequent diagnosis in Taiwan. The clinical characteristics of AIH in this area are unclear. The aim of this study was to elucidate the clinical features of AIH in Taiwan.

Methods. All the medical records of in-patients with the diagnosis of chronic hepatitis in our hospital from 1990 to 2001 were reviewed for the possibility of AIH. The clinical features, biochemical data, immunological presentations, treatments and survival of the patients were evaluated.

Results. Twenty-two patients (15 females and 7 males) were diagnosed as having AIH within 11 years. The median age at onset was 64 years (range: 17-77 years). Compared with female patients, male patients had older age (p = 0.001), shorter duration from initial presentation of symptoms to diagnosis (p = 0.015), lower serum levels of alkaline phosphatase (ALK-P, p = 0.022) and albumin (p = 0.043). Five (23%) patients presented with cirrhosis upon diagnosis. Compared with non-cirrhotic patients, cirrhotic patients had lower serum levels of alanine aminotransferase (p = 0.002), aspartate aminotransferase (p = 0.015), gamma-glutamyl transferase (G-GT, p = 0.002), albumin (p = 0.14), white cell counts (p = 0.009) and platelet counts (p = 0.002). Thirteen (59%) patients had concomitant clinical-pathological features of cholestatic liver disease (ALK-P ≥ 2 times of upper normal limit or pathological evidence of cholangiopathy). They had higher serum levels of ALK-P (p < 0.001) and G-GT (p = 0.004) than 9 non-cholestatic patients. There were no significant differences in survival between these groups. The prescribed initial and maintained prednisolone doses for our patients to control disease activity were 19 ± 15 mg and 8 ± 1 mg, respectively, which were lower than those recommended in Western countries. The remission rate to steroid treatment and relapse rate after discontinuing corticosteroids were 87.5% and 50%, respectively.

Conclusions. Compared with Western AIH patients, the AIH patients in Taiwan are older and more likely to develop cholestasis, and need a relatively lower dose of steroid for treatment. Owing to one quarter of the patients already having liver cirrhosis on diagnosis, AIH should be suspected in any Taiwanese patient with cryptogenic hepatitis or cirrhosis.

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Autoimmune hepatitis (AIH) is a chronic active hepatitis characterized by unrelenting hepatocellular necrosis and the presence of special serum autoantibodies. This disorder is not uncommon and has been well in vestigated in Western countries. Nevertheless, the role of AIH in the pathogenesis of chronic hepatitis is likely to be neglected in Taiwan that is an endemic area with hepatitis B and C viral infection. To the best of our knowledge, only sporadic cases of AIH have been reported in Taiwanese literature. The clinical characteristics of AIH here are unknown. The purpose of this study was to in vestigate the clinical characteristics of AIH in Taiwan.

Methods

Subjects

We retrospectively re viewed all the medical records of in pa tients with the diag nosis of chronic hepatitis (code of Internation al Classification of Disease: 571.40) upon dis charge from our hos pital from November 1990 to August 2001. Auto immune hepatitis was diag nosed based on the cri te ria pro posed by the Inter national Auto immune Hepatitis Group. It is a scoring sys tem com posed of gen der, ser um liver biochem is try, ser um glob ulin (or im muno glob ulin G), antinuclear an ti body (ANA), anti-smooth mus cle anti body (ASMA), anti-mitochondrial anti body (AMA), viral hepatitis mark ers, drug his tory, al co hol in take, liver histology, other autoimm un e dis ease and re sponse to ther apy. Definite AIH is diag nosed when the aggregate scores are greater than 15 before treat ment. For strict diag nosis, we fur ther ex cluded the prob able cases who had (1) neg a tive ser um ANA; (2) pos i tive ser um AMA, hepatitis B sur face an ti gen, or hepatitis C an ti body; (3) im aging ev idence of biliary tree ab nor mal i ties; (4) pos i tive cause of liver func tion dis ease, bio chem ical data, ser um ANA, ASMA, AMA and re sponse to treat ment were re corded for further eval uation.

The ser um auto antibodies, in cluding ANA, ASMA and AMA markers, were measured by an indirect immunofluorescence assay using the Fluoro-Kit™ (Incstar Corp. Stillwater, Min ne sota, USA) ac cord ing to the man u facturer’s in struc tions. Liver biochem ical tests were measured by an auto-analyzer (Hitachi Model 736 au to matic analy zer; Hitachi, Tokyo, Japan).

Statistics

Nu mer i cal data were ex pressed as mean ± SD. The Fisher’s ex act test or Mann-Whitney U test was used to com pare the pa rameters be tween groups as appropriate. The Kaplan- Meier model with log rank test was per formed for sur vival analy sis. A p value less than 0.05 was con sid ered statisti cally sig nificant.

Results

Twenty-two (1.62%) of the 1,357 pa tients with chronic hepatitis were diag nosed to have AIH, in cluding 11 definite and 11 prob able cases ac cord ing to the Scoring sys tem. The ini tial symp toms/signs are sum ma rized in Table 1. Of the 22 AIH pa tients, 15 (68%) were fe males and 7 (32%) were males (Table 2). The me dian age upon the on set of symp toms was 64 years (range: 17-77 years) whereas that upon
The diagnosis was 65 years (range: 17-77 years). The pretreatment characteristics and results of laboratory survey of all AIH patients are shown in Table 2.

Compared with female patients, the male patients displayed older age, lower serum albumin and alkaline phosphatase (ALK-P) levels upon the time of diagnosis.
sis (Table 3). Five patients (23%) presented with cirrhosis upon diagnosis. They had significantly lower serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (G-GT), albumin, white blood cell count and platelet count (Table 4). Thirteen (59%) patients

**Table 4. Comparison of pretreatment data between cirrhotic and non-cirrhotic patients with autoimmune hepatitis**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cirrhotic (n = 5)</th>
<th>Non-cirrhotic (n = 17)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) a</td>
<td>60 ± 22</td>
<td>53 ± 20</td>
<td>0.446</td>
</tr>
<tr>
<td>Female/male</td>
<td>3/2</td>
<td>12/5</td>
<td></td>
</tr>
<tr>
<td>Duration (weeks) b</td>
<td>209 ± 360</td>
<td>37 ± 69</td>
<td>0.762</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>100 ± 102</td>
<td>634 ± 394</td>
<td>0.002</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>154 ± 181</td>
<td>652 ± 479</td>
<td>0.015</td>
</tr>
<tr>
<td>ALK-P (U/L)</td>
<td>177 ± 127</td>
<td>230 ± 97</td>
<td>0.256</td>
</tr>
<tr>
<td>G-GT (U/L)</td>
<td>71 ± 37</td>
<td>335 ± 277</td>
<td>0.002</td>
</tr>
<tr>
<td>DB (mg/dl)</td>
<td>0.9 ± 0.6</td>
<td>5.2 ± 5.0</td>
<td>0.137</td>
</tr>
<tr>
<td>TB (mg/dl)</td>
<td>1.7 ± 0.6</td>
<td>6.8 ± 7.4</td>
<td>0.247</td>
</tr>
<tr>
<td>Globulin (g/dl)</td>
<td>4.2 ± 0.4</td>
<td>4.0 ± 1.0</td>
<td>0.636</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.8 ± 0.4</td>
<td>3.7 ± 0.6</td>
<td>0.014</td>
</tr>
<tr>
<td>IgG (mg/dl)</td>
<td>3,650 ± 1,143</td>
<td>2,875 ± 1,127</td>
<td>0.545</td>
</tr>
<tr>
<td>WBC (/cumm)</td>
<td>3,004 ± 1,465</td>
<td>6,048 ± 1,985</td>
<td>0.009</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.0 ± 3.5</td>
<td>12.5 ± 1.8</td>
<td>0.083</td>
</tr>
<tr>
<td>Platelet (/cumm)</td>
<td>79,600 ± 24,876</td>
<td>209,571 ± 81,149</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are expressed as Mean ± SD.

a: Age: upon diagnosis.
b: Duration: the time interval from initial symptoms to definite diagnosis.

**Table 5. Comparison of pretreatment data between cholestatic and non-cholestatic patients with autoimmune hepatitis**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cholestatic (n = 13)</th>
<th>Non-cholestatic (n = 9)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) a</td>
<td>53 ± 20</td>
<td>57 ± 21</td>
<td>0.512</td>
</tr>
<tr>
<td>Female/male</td>
<td>10/3</td>
<td>5/4</td>
<td></td>
</tr>
<tr>
<td>Duration (weeks) b</td>
<td>44 ± 77</td>
<td>122 ± 275</td>
<td>0.896</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>452 ± 378</td>
<td>600 ± 474</td>
<td>0.744</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>504 ± 506</td>
<td>590 ± 454</td>
<td>0.601</td>
</tr>
<tr>
<td>ALK-P (U/L)</td>
<td>269 ± 100</td>
<td>144 ± 55</td>
<td>0.004</td>
</tr>
<tr>
<td>G-GT (U/L)</td>
<td>381 ± 300</td>
<td>123 ± 92</td>
<td>0.014</td>
</tr>
<tr>
<td>DB (mg/dl)</td>
<td>3.2 ± 3.5</td>
<td>5.3 ± 5.8</td>
<td>0.295</td>
</tr>
<tr>
<td>TB (mg/dl)</td>
<td>3.4 ± 3.6</td>
<td>8.5 ± 8.9</td>
<td>0.095</td>
</tr>
<tr>
<td>Globulin (g/dl)</td>
<td>3.9 ± 0.9</td>
<td>4.2 ± 1.0</td>
<td>0.331</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.7 ± 0.7</td>
<td>3.2 ± 0.5</td>
<td>0.095</td>
</tr>
<tr>
<td>IgG (mg/dl)</td>
<td>2,954 ± 1,399</td>
<td>3,106 ± 774</td>
<td>0.918</td>
</tr>
<tr>
<td>WBC (/cumm)</td>
<td>5,308 ± 2,455</td>
<td>5,693 ± 2,069</td>
<td>0.804</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.0 ± 3.5</td>
<td>12.5 ± 1.8</td>
<td>0.247</td>
</tr>
<tr>
<td>Platelet (/cumm)</td>
<td>176,500 ± 70,304</td>
<td>174,111 ± 115,004</td>
<td>0.720</td>
</tr>
</tbody>
</table>

Data are expressed as Mean ± SD.

a: Age: upon diagnosis.
b: Duration: the time interval from initial symptoms to definite diagnosis.

Abbreviated as Table 1.
who had a more than 2-fold increase of ALK-P and/or histologic evidence of biliary tree injury were regarded as cholestatic group (Table 5). They had higher serum levels of ALK-P and G-GT compared with non-cholestatic patients (Table 5).

Four patients were associated with autoimmune diseases, including 3 with Sjögren’s syndrome and one with systemic lupus erythematosus.

Steroid therapy was instituted to 16 patients. Two patients lost follow-up after initial treatment. The remaining 14 patients responded well (a decline of ALT) in an average of 27 ± 13 days. The ALT level before steroid therapy in initial treatment was 697 ± 386 U/L and responded to the therapy to fall to 71 ± 57 U/L. They expressed normal liver enzyme levels (87.5%) after an average of 57 ± 22 days. The average time of maintenance was 49 ± 40 months. The mean initial and main-tained doses of prednisolone were 19 ± 15 mg and 8 ± 1 mg/day, respectively. Among the 14 patients, 1 patient discontinued steroid treatment due to persistent normalization of liver biochemistry test; 4 patients under went tapering of steroids upon the end of our follow-up; whereas 7 pa-tients (50%) suffered from aggravation of liver biochemistry test data after tapering steroids. Steroid therapy was not prescribed to 6 patients, because 5 of them were cirrhotic patients with nearly normal liver enzyme levels and 1 patient lost follow-up after clinical diagnosis.

Liver biopsy was performed in 12 pa-tients, and had evidence of periportal necroinflammation (in surface hepatitis) (Fig. 1) in all. Concomitant non-specific biliary tree damage was found in 9. Of these 9 patients, 6 responded to steroid therapy well with normalization of liver enzyme levels. The other 3 patients did not receive steroid therapy because of initial diagnosis of cirrhosis in 2 and loss of follow-up in 1.

Three patients died of liver cirrhosis with esophageal variceal bleeding, hepatic decompensation, and pulmonary sepsis, 1 patient lost follow-up after diagnosis of cirrhosis, 2 patients lost follow-up after initial treatment. There was no significant difference in survival between male and female patients (81 ± 43 vs. 65 ± 9 months, p = 0.6769).

**Discussion**

AIH is a disease of unknown etiology, characterized by female predominance, hypergammaglobulinemia, circulating antibodies, hepatocytic damage, and marked response to immunosuppressive therapy.\(^1,2\) Accurate diagnosis for AIH is indeed important for an appropriate therapy.\(^7\) However, the spectrum of autoimmune hepatic injury varies markedly from pure hepatocytic to biliary epithelial damage,\(^1,8,9\) which occasionally makes the distinction quite difficult. Since the current study was performed retrospectively, to avoid cases with controversies regarding adequate study or indefinite diagnosis, out-patients and those with AMA positivity were excluded. Selection bias may be present under such a setting, but the remaining cases can be evaluated as an AIH group undoubtedly.

Autoimmune hepatitis can be classified as type 1 with the presence of ANA, ASMA and type 2 with liver-kidney microsomal antibody (LKM1).\(^10,11\) Furthermore, the relation-ship of AIH classification and clinical characteristics to HLA-DR3 and -4 status have been reported.\(^12\) Due to the retrospective nature of our study, how ever, LKM1 and HLA tests were not
performed upon initial presentation of the patients.

In our series, female to male ratio was 2.1, which was sig
ificant lower than that reported for the Japa
ese (ratio: 6:1)\textsuperscript{13} and for the West erns (ratio: 8:1).\textsuperscript{14} It may count that our ho
spital serves mainly for veter ans. Al though AIH usu
ally affects young females and the meno paus e women in West ern areas,\textsuperscript{3,14} our AIH pa
tients seemed older at on set (54 ± 20 years). Sim ilarly, two Japa
ces e ries re ported the on set at older age, too (50 and 70 years, re spec tively).\textsuperscript{13,15}

Thirteen of our AIH patients had e l e vated ALK-P and G-GT lev els and/or cholesterolopathy ver ified by pa
thology. How ever, the fol low ing re asons still sup
port the di ag no sis of AIH in these pa tients: 1) high ti
ter of ANA with out AMA; 2) el e vated se rum lev els of im
munoglobulin G in stead of M, which is con sis tent
with the fea tures of AIH rather than pri mary biliary cirrho
sis (PBC); 3) the ab sence of biliary tree dis ease
to de velop over a me dian fol low-up of 91 months; 4) ex cept 2 pa
tients lack ing follow-up, those who re
ceived corticosteroid ther apy sig nificant im proved
with nor mal iza tion of liver bio chem is try data. This
further sup ported the di ag no sis of AIH; 5) no
biliary tree ab nor mal ity iden ti fied by sonography. The
cause of a higher per cent age of cho lestatic pa tients in
our AIH patients, how ever, re mains to be clari fied.

Auto immune cholangitis can be very sim ilar to pri
mary biliary cir rhosis in non-cholestatic pa tients, ex cept for cirrhosis (PBC); 3) the ab sence of biliary tree dis ease
to de velop over a me dian fol low-up of 91 months; 4) ex cept 2 pa
tients lack ing follow-up, those who re
ceived corticosteroid ther apy sig nificant im proved
with nor mal iza tion of liver bio chem is try data. This
further sup ported the di ag no sis of AIH; 5) no
biliary tree ab nor mal ity iden ti fied by sonography. The
cause of a higher per cent age of cho lestatic pa tients in
our AIH patients, how ever, re mains to be clari fied.

Auto immune cholangitis can be very sim ilar to
PBC re gard ing its clin i cal, bio chem i cal, and histo
pathological fea tures ex cept neg a tive AMA and pos i
tive ANA. Its clas si fi ca tion in the field of au
to im mune liver disease remains un cer tain.\textsuperscript{17,18} Au toim mune
cholangitis may be a vari ant of pri mary biliary cirrho
sis.\textsuperscript{18,19} Though un cer tainty ex ists,\textsuperscript{20-22} all of our
pa tients, ex cept 5 cirrhotic pa tients, had at least 3-fold
el evation of alanine transaminase lev els and/or patho
logical evidence of interphase hepatitis. Con se
quently, the di ag no sis of AIH with cho lestatic fea tures
rather than au to im mune cholangitis was es tab lished.

In the West ern ex per i ences, the rec ommended ini
tial dose of prednisolone is 60 mg/day, and the main te
nance dose is 20 mg/day.\textsuperscript{2} In con trast, we pre scribed
the lower doses for the AIH pa tients (the ini
tial and main te nance doses of prednisolone were 19 ± 15 and
8 ± 1 mg, re spec tively). The re mis sion rate in our se
ries was 87.5%, which was com pa ra ble with that of a

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