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Clinical features of elderly Chinese patients with autoimmune hepatitis

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Background/aims: *To study the clinical features of elderly Chinese patients with autoimmune hepatitis.* ***Materials and Methods:*** *The clinical features of 36 patients diagnosed at age >60 years were compared with those of 39 patients aged <50 years.* ***Results:*** *The M:F ratio was 1:35 (>60 years) vs. 3:36 (<50 years). The patients >60 years had a higher frequency of cirrhosis at presentation than the patients <50 years (52.8% vs. 15.4%, p=0.001). The patients >60 years also had a significantly increased incidence of ascites at presentation (41.7% vs. 10.3%, p=0.001) and lower serum albumin levels (p=0.037). There were significant differences between older and younger patients with respect to the frequencies or titers of anti-nuclear antibody (46.2% vs. 83.3%, p=0.011). HLA DR3 positivity occurred more frequently in the patients <50 years than in those >60 years (59.0% vs. 19.4%, p<0.001), whereas HLA DR4 occurred more often in the patients >60 years (63.9% vs. 25.6%, p=0.001). Treatment failure occurred more frequently in the patients <50 years (28.2% vs. 9.1%, p=0.041). However, there were no significant differences between the groups with respect to mode of onset, other clinical signs at presentation biochemical parameters, and smooth muscle antibody positivity.* ***Conclusion:*** *Elderly patients have a greater frequency of cirrhosis at presentation, anti-nuclear antibody, HLA DR4 positivity than patients <50 years, and they have a lower occurrence of treatment failure. Conventional corticosteroid regimens may be an effective management for older patients with autoimmune hepatitis.*

Key words: Autoimmune hepatitis, elderly patients, cirrhosis

Otoimmun hepatitli yaşlı Çin'li hastaların klinik özellikleri

Giriş ve Amaç: *Otoimmun hepatitli yaşlı Çin'li hastaların klinik özelliklerinin araştırılması amaçlanmıştır.* ***Gereç ve Yöntem:*** *Altmış yaşından sonra tanı alan 36 hastanın özellikleri 50 yaşından önce tanı almış olan 39 hastanınki ile karşılaştırıldı.* ***Bulgular:*** *Erkek - kadın hasta oranı 1:35 (>60 yaş) ve 3:36 (<50 yaş) bulundu. Yaşlı hastalarda başvuruda siroz bulunma sıklığı genç olanlara göre anlamlı olarak yüksek (%52,8 - %15,4; p=0.001) bulundu. Ayrıca yaşlı hastalarda başvuruda assit (%41,7-%10,3; p=0.001) ve hipoalbuminemi (p=0.037) olma olasılığı daha yüksek bulundu. Yaşlı ve genç hastalar karşılaştırıldığında anti-nükleer antikor titrelerinin dağılımı (%46.2 - %83.3; P=0.011) farklı bulundu. Genç hastalarda HLA-DR3 sıklığı daha yüksek (59.0% - 19.4%, P<0.001) bulunurken, yaşlı hastalarda HLA-DR4 sıklığı daha yüksek (63.9% - 25.6%, P=0.001) bulundu. Genç hastalarda tedavi başarısızlığı daha sık görülürken (%28,2 - %9,1; 0,041), gruplar arasında hastalık başlangıcı, klinik prezentasyondaki özellikler, biyokimyasal özellikler ve düz kas antikor pozitifliği benzer bulundu.* ***Sonuç:*** *Yaşlı hastalarda, başvuruda daha sık siroz, anti-nükleer antikor pozitifliği ve HLA DR4 pozitifliği ile karşılaşılmaktadır ve tedavi başarısızlığı daha nadirdir. Yaşlı hastalarda konvansiyonel steroid tedavilerinin kullanılması etkin bir seçenek olabilir.*

Anahtar kelimeler: Otoimmun hepatit, yaşlı hastalar, siroz

INTRODUCTION

Autoimmune hepatitis (AIH) is an unresolving inflammation of the liver of unknown cause. It is characterized by the presence of interface hepatitis and portal plasma cell infiltration on histologic examination, and laboratory findings show hypergammaglobulinemia with positive autoantibodies

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at high titers. The diagnosis is further supported when the criteria issued by the international autoimmune hepatitis group (IAIHG) are met.

AIH was originally described in peripubertal females (1), and for many years it was considered to be a condition that mainly affected young women and is rarely seen in older people (2). With the increasing aging of the population and improvement of diagnostic facilities, AIH has also been diagnosed more and more in elder patients. Several groups have reported on characteristics of elderly patients with AIH (3-7). However, there have been no reports on the clinical characteristics of elderly Chinese patients with AIH yet.

Therefore, the aim of the present study was to evaluate the general status, clinical manifestations, laboratory findings, severity of disease, response to treatment and outcome of 36 elderly Chinese patients diagnosed with type 1 AIH by comparing patients presenting above the age of 60 years and below the age of 50 years.

PATIENTS and METHODS

All patients were either hospitalized or outpatients at our hospital over the past six years. A total of 75 patients with AIH were included in this study. The diagnosis of AIH was made according to the criteria of the International Autoimmune Hepatitis Group (IAIHG). Of the 75 patients, 36 were diagnosed with AIH at ages above 60 years and 39 were diagnosed at age less than 50 years old. The diagnosis of AIH was based on criteria recommended by the IAIHG in the revised scoring system in 1999 (8) (definite AIH >15 scores before treatment and >17 after treatment; probable AIH 10-15 before treatment and 12-17 after treatment) and a simplified IAIHG set of diagnostic criteria (definite AIH >6 scores, probable AIH=5 scores) in 2008 (9). Other possible causes of liver diseases including viral hepatitis, significant alcohol intake (>40 g/day), the consumption of any medication that might conceivably be associated with liver injury, clinical or radiological data suggesting sclerosing cholangitis were excluded from this study.

Observation

Serum levels of total bilirubin (T-bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin (ALB), gamma glutamyl transferase (γ-GT) as well as immune findings such as immunoglobulin M (IgM), immunoglobulin A (IgA), immunoglobulin G (IgG), anti-nuclear antibody (ANA), smooth muscle antibody (SMA), and needle liver biopsy were analyzed. The diagnosis of cirrhosis required evidence of fibrosis and the presence of at least one complete regenerative nodule. HLA-DR3 and DR4 were determined in each individual by restriction fragment length polymorphism or polymerase chain reaction with sequence specific primers according to methods reported previously.

Treatment Regimens and Outcome

All 39 younger sufferers and 33 out of 36 elderly subjects were treated with prednisolone monotherapy or combined with azathioprine. Treatment outcomes between the patients aged >60 years and those aged <50 years were compared. Treatment was continued until the pre-defined endpoints of remission or treatment failure had been achieved. Remission connoted absence of symptoms, improvement of serum AST levels to normal or near normal (less than twice the upper limits of normal), and histological improvement to minimal or no inflammatory activity shown by repeated liver biopsy. Medication was then withdrawn in a gradual fashion over a 6-week period. Treatment failure connoted worsening of clinical, laboratory and/or histological features despite compliance with therapy. Doses of medication were then increased in accordance with a previously published protocol. Reappearance of symptoms and increase in the serum AST level to more than threefold normal after drug withdrawal indicated relapse, and these findings justified re-treatment. Absence of symptoms and serum AST levels that were normal or below the relapse threshold after drug withdrawal connoted a sustained remission. Clinical, laboratory or histological findings during therapy that indicated residual disease activity which had not worsened or improved sufficiently to satisfy endpoint criteria warranted continued treatment (10).

Statistical Analysis

The Fisher exact test was used to compare dichotomous variables, and the unpaired t-test was used to compare differences in the means of continuous variables. A p-value of 0.05 was used to determine statistical significance. Data are presented as the mean±standard error of the mean.

RESULTS

Patients

A total of 36 elderly patients were diagnosed with AIH, and the clinical features of these patients are

Table 1. Mode of onset and presenting signs and symptoms

	Age at presentation(years) <50 (N=39)	>60 (N=36)	p-value
Mode of onset			
Acute	12 (30.8%)	4 (11.1%)	0.038
Insidious	23 (59.0%)	29 (80.6%)	0.043
Asymptomatic	4 (10.3%)	3 (8.3%)	0.775
Signs and symptoms			
Jaundice	25 (64.1%)	24 (66.7%)	0.149
Pale stools/dark urine	22 (56.4%)	14 (38.9%)	0.237
Abdominal distension	14 (35.9%)	11 (30.6%)	0.624
Ascites	4 (10.3%)	15 (41.7%)	0.001
Fatigue	35 (89.7%)	27 (75.0%)	0.092
Pruritus	4 (10.3%)	2 (5.6%)	0.453
Arthralgia	6 (15.4%)	3 (8.3%)	0.348
Upper GI bleeding	2 (5.1%)	2 (5.6%)	0.934
Encephalopathy	2 (5.2%)	3 (8.3%)	0.578

Table 2. Details of patients with a laboratory at diagnosis

	Age at presentation (years) <50	>60	p-value
Gender, female (%)	36 (92.3)	35(97.2)	0.344
Median months to diagnosis (range)	24.2 (0.5-108)	24.7 (4-120)	0.862
Total bilirubin (μmol/L)	50.1±19.6	43.2±25.4	0.221
ALT (ULN)	201.6±150.9	205.9±124.6	0.095
AST (ULN)	230.8±108.7	200.6±118.1	0.076
ALP (ULN)	136.4±86.8	146.9±39.7	0.097
GGT (ULN)	121.9±103.2	112.8±82.8	0.146
ALB (g/L)	33.5±5.2	27.2±7.1	0.037
Serum immunoglobulin, g/L			
Immunoglobulin M	146.6±79.7	138.5±56.5	0.214
Immunoglobulin A	398.3±24.9	397.1±188.3	0.231
Immunoglobulin G	3766.2±1047.2	3562.3±1372.9	0.332
Autoantibody			
ANA	18 (46.2%)	30 (83.3%)	0.011
SMA	31 (79.5%)	27 (75.0%)	0.643
Cirrhosis at presentation	6 (15.4%)	19 (52.8%)	0.001
HLA DR3 n (%)	23 (59.0%)	7 (19.4%)	<0.001
HLA DR4, n (%)	10 (25.6%)	23 (63.9%)	0.001

ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. ALP: Alkaline phosphatase. GGT: Gamma glutamyl transpeptidase. ALB: Albumin.

shown in Tables 1 and 2. The M:F ratio was 1:35 (>60 years) (35/36, 97.2%). The mean age at final diagnosis was 66.5 years (range 60-74 years), and the time interval from initial symptoms or preliminary diagnosis to final diagnosis of AIH was 24.7 months (range 4-120 months). The most fre-

quent symptoms reported were fatigue (27/36, 75.0%) and jaundice (24/36, 66.7%). Fifteen patients had ascites (15/36, 41.7%). 19 patients had cirrhosis (19/36, 52.8%). All the elderly patients were found to have elevated AST and IgG levels on routine physical examination. After ANA and SMA measurements and liver biopsy, the diagnosis of AIH was made.

Clinical Feature and Laboratory Data at Presentation

The presenting clinical signs and symptoms were very similar between the two groups. There was, however, a significantly higher frequency of cirrhosis in the elder patients at presentation. Patients' clinical features are shown in Table 2. As expected, a female predominance was seen in both the older AIH group (35/36, 97.2%) and younger AIH group (36/39, 92.3%). There was no significant difference in the modes of presentation (acute, insidious, or asymptomatic) between the two groups. There was, however, a significantly higher frequency of ascites in the elder patients at presentation (41.7% vs. 10.3%, p=0.001). This appeared to be related to the presence of cirrhosis, the incidence of which was significantly different between the two groups (52.8% vs. 15.4%, p=0.001). Serum albumin level was lower in elderly patients (p=0.037). There were no significant differences between the groups with respect to mode of onset, other clinical signs at presentation biochemical parameters, and SMA positivity. There were significant differences between older and younger patients with respect to frequencies or titers of ANA (46.2% vs. 83.3%, p=0.011). Analysis of the data for all patients who had been HLA typed revealed a higher frequency of the DR3 haplotype in the patients aged <50 years (59.0% vs. 19.4%, p<0.001). HLA DR4 occurred more frequently in the patients aged >60 years than in those aged <50 years (63.9% vs. 25.6%, p=0.001).

Treatment and Clinical Outcome

Treatment and clinical outcome are shown in Table 3. In terms of treatment, 3 of elderly individuals had received none, whilst all younger sufferers were treated with prednisolone with or without azathioprine. The longest duration of follow-up period was 8 years and the shortest was 6 months, while 76.5% of these patients were on follow-up for more than 4 years. 33 elderly subjects received treatment with or without azathioprine. During the follow-up, one developed cirrhosis, whilst the remaining had chronic hepatitis or cirrhosis. The outcomes for the three elderly untreated subjects were as follows: one died from HCC and the two survivors were found to have continued disease but received no immunosuppressive therapy. There were no significant differences between the two groups with respect to proportions of patients receiving different regimens of initial or maintenance therapy. More than 50% of patients in each group showed a complete initial response to therapy. However, treatment failure occurred significantly more frequently in the younger patients (28.2% vs. 9.1%, p=0.041).

DISCUSSION

We described a group of 36 elderly patients with AIH who presented for the first time at age 60 years or older. Although AIH has been assumed to be a disease of middle-aged woman, more and more cases have been identified in older patients. This increase may be related to increasing attention to this disorder not only among specialists but also among general physicians who were not familiar with AIH before, owing to the revised scoring system and the simplified IAIHG set of diagnostic criteria for AIH proposed in 1999 and 2008, respectively. This increased interest has provided an opportunity to properly diagnose many cases in ol-

Table 3. Treatment outcomes in the young and elderly age groups

Treatment Outcomes	Treated patients <50 years (N =39)	Treated patients >60 years (N=33)	p-value
Remission	22 (56.4%)	20 (61.5%)	0.719
Relapse	17 (17/22)	15 (15/20)	0.863
Sustained remission	5 (5/22)	5 (5/20)	0.863
Treatment failure	11 (28.2%)	3 (9.1%)	0.041
Continued treatment	6 (15.4%)	10 (30.3%)	0.129
Hepatic death	1 (2.6%)	1 (3.0%)	0.905

der patients as well. Czaja and Carpenter (11) have shown that clinical characteristics of AIH in elderly patients are different compared to those in younger patients in the United States. However, there have been no reports about the characteristics of patients with AIH in older age in China.

In this study, our initial result revealed no differences in biochemical data between patients with AIH aged >60 years and aged<50 years. In contrast, the patients aged >60 years had a higher frequency of cirrhosis at presentation than those aged <50 years. Therefore, our findings suggested that elderly patients may progress to cirrhosis more rapidly than young adults with type 1 AIH, or liver disease was more indolent and therefore more advanced at the time of detection in older patients. The latter possibility was favored because the elderly patients did not have laboratory evidence of more severe inflammatory activity at presentation than the young adults. Rapid progression to cirrhosis is usually associated with laboratory indices that reflect severe disease activity (12,13), and it is frequently associated with a poor outcome (14). Other experiences that have indicated delay in the diagnosis and treatment of the elderly with AIH have also recognized the high frequency of cirrhosis in these patients (15). These observations support the hypothesis that the elderly have an indolent aggressive liver disease that frequently progresses to cirrhosis prior to diagnosis. Irrespective of mechanism, the present study and that by Czaja and Carpenter (11) revealed that increased fibrosis is a characteristic feature of AIH in older patients. However, the exact cause is not clear, although differences in patients' genetic and environmental backgrounds may play a role.

We also found that the significant difference was in the proportion of patients with ascites at accession, which was greater in the older patients. The reason was obviously due to either a higher incidence of cirrhosis in older patients or a difference in the incidence of hypoalbuminaemia between the two groups. A possible explanation for the increased incidence of ascites in aged >60 patients is an enhanced susceptibility to the physiological effects of fibrosis/cirrhosis with increasing age. This concept is supported by the recent observations that senescence is associated with pseudocapillarization of the hepatic sinusoidal endothelium, and that this in turn results in increased rigidity of the sinusoid and increased resistance to blood flow (16,17). These findings could in part explain the increased prevalence of ascites with or without cirrhosis being apparent on biopsy specimens.

Our elderly patients were distinguished from the young adults with type 1 AIH by having a significantly greater frequency of HLA DR4 and lower occurrence of HLA DR3. In Europe and North America, susceptibility to AIH type 1 is conferred by the possession of HLA DR3 and DR4, both heterodimers containing a lysine residue at position 71 of the DRB1 polypeptide and the hexameric amino acid sequence LLEQKR at positions 67-72 (18,19). These HLA associations may be the molecular footprints of the prevailing environmental triggers that precipitate AIH type 1 in different environments. This molecule cradles the triggering antigen, and the complex activates the CD4+T helper cells that propagate the immune response. Multiple antigens may have structural or conformational similarities that favor their presentation in these class II MHC molecules, and numerous homologous peptides may trigger the same disease. A low frequency of HLA DR4 in adolescent and early adulthood patients with type 1 AIH may indicate participation of other factors besides HLA DR status in the pathogenesis. Recently, cytotoxic T-lymphocyte antigen-4 and programmed cell death-1, which are co-stimulatory molecules, were reported to be associated with the pathogenesis of AIH (8,10,20). Impairment of these co-stimulatory molecules results in downregulation of regulatory T cells and breakdown of self-tolerance. Similar to the case of primary biliary cirrhosis, interactions among several genetic factors may be important in the pathogenesis of AIH (21). Thus, our results suggest that the restricted range of peptides that can trigger the disease in patients with HLA DR3 may implicate an etiologic factor that is less frequently encountered in the elderly and more likely to generate a vigorous immune response in the young. This transition in susceptibility occurred at the age of 60 years above.

This study confirms that remission can be induced and maintained in most AIH patients on the standard corticosteroid-based immunosuppression that has been used for several decades. Despite 52.8% of elderly patients have been diagnosed with cirrhosis at presentation, which is high compared with 15.4% in patients aged <50 years consistent with other data showing that the presence of cirrhosis does not affect steroid responsiveness. These findings are in accord with other experien-

ces that have emphasized the responsiveness of the elderly to conventional treatments. Histological cirrhosis is not associated with an impaired treatment response (22-24). In this study, we now extend these observations by indicating that the elderly patients have a lower frequency of treatment failure than the young adults with the disease. However, the pathogenic mechanism is unclear. Like most autoimmune diseases, the theory and research have been concentrated on genetically susceptible hosts, T cells abnormalities. Elderly patients with HLA DR4 may be more dependent on cytokines modified by corticosteroid therapy than patients with HLA DR3 (25). Aging alters immune responsiveness by decreasing the expression of HLA class II molecules and reducing stimulation and proliferation of antigen-stimulated T cells (26). Whether the age-related immune transitions may affect the treatment outcome of type 1 AIH needs further study.

In conclusion, elderly patients have a greater frequency of cirrhosis at presentation and HLA DR4 than patients <50 years, and they have a lower occurrence of treatment failure. Conventional corticosteroid regimens may be an effective management of older patients with AIH.

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