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Evaluation of patients with autoimmune hepatitis: eleven years of experience

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Summary

Aim: This study aimed to review a series of patients with autoimmune hepatitis in terms of disease pattern, laboratory results, treatment outcomes and adverse effects of treatment.

Material and Method: Children with autoimmune hepatitis were retrospectively reviewed. In all patients, viral and metobolic etiologies were excluded. Patients were classified as type-1, type-2 and non-classified type, as well as acute and chronic groups. Treatment response and cessation of treatment were evaluated.

Results: Patients were beetween 4 and 17 years old (12±2.68 years). Twenty patients were female, 11 patients were male. Seventeen percent of the patients were in the acute group and 14% were in the chronic group; 18% were in the type-1 group, 6% were in the type-2 group and 7% were in the non-classified type group. Deflazacort was started in all patients. Azothiopurine (2 mg/kg/day) was added in 10 patients with late response at the end of the third month. Deflazacort dosage was decreased at 6-8 weeks intervals and continued at a maintenance dosage of 5 mg/day. After a two-year period complete response was obtained in 24 patients and partial response was obtained in 5 patients. No response was obtained in 2 patients. During the nine-year follow-up period, treatment was ended in 6 patients. In one patient, there was a recurrance in 6 months; the remaining 5 patients are still being followed up without a problem. Despite treatment, portal hypertension was observed in 5 patients.

Conclusions: Early diagnosis and treatment of childhood autoimmune hepatitis can decrease the risk of progression to cirrhosis and can increase the survival. Deflazocort can be a choice instead of prednisolone because of its efficiency in treatment and lesser side effects. *(Turk Arch Ped 2012; 47: 29-34)*

Key words: Autoimmune hepatitis, azothiopurine, children, deflazocort

Introduction

Autoimmune hepatitis (AIH) is a chronic, progressive, inflammatory hepatic disease with unknown cause. It is characterised by the presence of various autoantibodies in the serum, high level of gammaglobulin and mononuclear cell infiltration in the periportal or portal area histopathologically (motheaten necrosis) (1-5). According to immunoserologic findings four types of AIH were defined as type 1, type 2, type 3 and undefined autoimmune hepatitis (6-11). Autoimmune hepatitis occurs mostly at the ages of 10-20 years. Since it rapidly progresses to cirhossis, if untreated, early diagnosis and treatment is very important to prevent this problem. The main treatment is corticosteroids. However, combined treatment with an additional immunosupressor drug gains importance to prevent side effects of chronic corticosteroid treatment (6,8). In our study, we examined clinical and laboratory findings, treatment responses and follow-up outcomes in 31 patients with autoimmune hepatitis.

Material and Method

35 subjects with a diagnosis of autoimmune hepatitis were followed up between January 1998 and December 2009 in the Division of Pediatric Gastroenterology in Şişli Etfal Education and Research Hospital. One subject was excluded from the study because of rapid progression to acute hepatic failure at presentation and three subjects were excluded because of decompensated AIH. The demographic features of the subjects, clinical and laboratory findings, Human Leucocyte Antigene-HLA types, hepatic biopsy results, treatment responses and outcomes during follow-up were examined retrospectively from the files. The diagnosis of autoimmune hepatitis was made in accordance with “International

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Autoimmune Hepatitis Group" criteria (12,13). The subjects with positive antinuclear antibody (ANA) and/or positive smooth muscle antibody (SMA) were classified as type-1 AIH, the subjects with positive "liver-kidney microsomal" type-1 antibody (LKM-1) were classified as type 2 AIH, the subjects with positive "soluble liver antigene" antibody (anti-SLA) were classified as type 3 AIH and the subjects without autoantibody were classified as undefined AIH. The subjects presenting with findings similar to the findings of acute viral hepatitis (fever, jaundice, pain in the right upper abdominal quadrant and transaminase levels higher than 500 IU/L) were classified as acute form and the subjects presenting with findings including loss of appetite, ascites, hepatomegaly-splenomegaly and intermittent jaundice were classifed as chronic form. In all subjects, complete blood count, hepatic function tests, albumin, total protein, immunglobulins, prothrombin time, alpha-1 antitrypsin, ferritin, copper, seruloplasmin level and the amount of excretion of copper in 24-hour urine was measured in the Biochemistry Laboratory in our hospital. Hepatitis A, B, C markers, cytomegalovirus and Ebstein-Bar virus (EBV) serology was assessed in the Microbiology Laboratory in our hospital. Antinuclear antibody, SMA, antimitochondrial antibody (AMA), LKM-1, Anti-SLA antibodies were examined in the Microbiology Laboratory in Cerrahpaşa Medical Faculty by indirect immunflourescence method. Class I and II HLA antigens were investigated in the Blood Center of the same hospital by "complement-dependent lymphomicrotoxicity" test method. For each antibody a level of >1/40 was considered to be high. Hepatic and splenic dimensions and parenchimal status were examined by abdominal ultrasonography in all subjects. Endoscopy was performed in the subjects in whom splenomegaly was found. Needle biopsy of the liver was performed before treatment in 27 subjects and four months after treatment was started in 4 subjects with abnormal coagulation tests. The biopsies were evaluated by the same pathologist in the division of pathology in our hospital using necroinflammatory efficiency grade and fibrosis grade "Knodell Histological Activity Index" (14,15).

After treatment was started the subjects were evaluated according to the clinical and biochemical values monthly. Azathioprine (AZA) was added to treatment in subjects with values 1,5-2 fold higher than the normal value at the third month. The subjects whose serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels normalized in 6-24 months were considered to have complete response. The subjects whose ALT and AST levels did not normalize up to two years, but decreased compared to the baseline level were considered to have partial response. No decrease in the 2-year follow-up period was considered to be unresponsiveness. Increase in ALT and AST after response to treatment or after the treatment was discontinued was considered to be recurrence of the disease (16). All subjects were examined in terms of side effects and other autoimmune diseases (Celiac disease, type-1 diabetes mellitus, autoimmune thyroiditis).

Statistical Analysis

SPSS 2000-10,0 program was used in the statistical analysis. Comparison of the laboratory values was performed using Annova multiple comparison test.

Results

20 (64.5%) of 31 patients included in the study were female and 11 (35.5%) were male. Their ages ranged between 4 and 17 years (12±2.68 years). According to the clinical findings at presentation 17 patients (54.8%) had acute type and 14 (45.2%) had chronic type. The period between the beginning of the symptoms and the time when the diagnosis was made was 2-25 months (average 10 months). According to autoantibody positivity 18 patients (58%) were considered as type-1, 6 patients (19.5%) were considered as type-2 and 7 patients (22.5%) were considered as undefined AIH. We had no type-3 subject. HAV IgM and IgG were positive in 4 subjects, EBV IgM was positive in 6 subjects, Coombs positive autoimmune hemolytic anemia was present in 2 subjects and familial Mediterranean fever was present in one subject. Since magnetic resonance (MR) cholangiography was found to be normal in 4 subjects with positive antimitochondrial antibody and cholestasis, primary sclerosing cholangitis was excluded. Clinical and physical examination findings of the subjects are shown in Table 1. When biochemical data were examined according to autoimmune hepatitis types: increase in GGT, total bilirubin, immunglobulin G, total protein and cholesterol was found to be more prominent in type-1. Increase in AST-ALT (0-35 IU/L, 0-45 IU/L) was found to be more prominent in type-2. Prolongation in prothrombin time was found to be more prominent in the undefined type. However, there was no statistical difference between the data (Table 2). Hypoalbuminemia was found in 11 (35%) subjects (alb<3.5 gr/dL), prolongation in prothrombin time was found in 4 subjects (13%) and decrease in thrombocyte count (<150 000/mm^3) was found in 5 subjects. Positive ANA was found in

Table 1. Reasons for presentation and physical examination findings

Reasons for presentation	**n (%)**
Jaundice	22 (71%)
Abdominal distention	5 (16.1%)
Pruritus	2 (6.4%)
Malaise	2 (6.4%)
Physical examination findings	**n (%)**
Hepatomegaly	24 (77.4%)
Splenomegaly	17 (54%)
Ascites	3 (6.4%)

Table 2. Biochemical measurements and comparison by types in subjects with autoimmune hepatitis

Measurement	Type 1 (n=18) (mean±SD)	Type 2 (n=6) (mean±SD)	Undefined type (n=7) (mean±SD)	p
AST IU/L	528.05±600.19	944.5±1151.4	584.0±510.3	0.854
ALT IU/L	410.11±430.72	635.33±687.63	455.5±435.78	0.453
GGT IU/L	169.61±246.42	66.1±24.25	55.7 5±24.37	0.543
ALP IU/L	592.77±494.21	444.5±169.01	440.0 ±220.69	0.355
T. Biluribin	5.2±2.69	4.5±2.67	3.7±0.69	0.412
Prothrombin t.	65.55±19.59	68.33±14.62	53.75 ±22.78	0.312
T. protein	8.26±1.54	7.83±0.41	7.47 ±1.12	0.542
Albumin	3.70±0.69	3.73±0.59	3.37 ±0.72	0.542
Globulin	4.62±1.32	3.9±0.57	4.05 ±1.19	0.468
IgG mg/l	2810.41±1306.63	2370.66±803.77	2414.25±2102	0.664
IgA mg/l	288.58±124.60	177.50±68.14	250.12±231.27	0.293
IgM mg/l	281.76±170.23	206.83±87.59	212±145.96	0.543
Cholesterol	168.11±170.55	140.83±34.75	133.25 ±61.08	0.787
Triglyceride	108.28±61.61	96.16±36.64	100.51±64.13	0.886
HLA	A24.9. A26. A32. DRB1.15	A26. B51. DRB1.11.	A32 ve DRB1.04	

AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transpeptidase, ALP Alkaline phosphatase, HLA: human leucocyte antigene, AIH: autoimmune hepatitis, SD: standard deviation.

Table 3. Histopathological findings of liver biopsy and differences between acute disease, chronic disease and autoimmune hepatitis types

	Acute (n=14)	Chronic (n=17)	Total (n=31)	Type 1 (n=18)	Type 2 (n=6)	Undefined type (n=7)
Portal inflammation						
Mild	9 (64.2%)	5 (29.4%)	14 (45.1%)	10 (55.5%)	1 (16.6%)	2 (28.5%)
Moderate	8 (57%)	4 (23.5%)	12 (38.7%)	5 (27.7%)	2 (33.3%)	4 (57%)
Severe	2 (14.3%)	3 (17.6%)	5 (16.1%)	2 (16.6%)	2 (50%)	1 (14.3%)
Fibrosis						
Mild	6 (42.8%)	4 (23.5%)	10 (32.3%)	8 (44.4%)	2 (33.3%)	2 (28.5%)
Moderate	5 (35.7%)	7 (41%)	12 (38.7%)	7 (38.8%)	3 (50%)	4 (57%)
Prominent	2 (14.3%)	3 (17.6%)	5 (16.1%)	3 (16.6%)	1 (16.6%)	1 (14.3%)
Cholestatic changes	1 (7%)	3 (17.6%)	4 (13%)	2 (11%)	0	2 (28.5%)

6 subjects (19.5%), positive SMA was found in 16 subjects (51.6%) and positive LKM-1 was found in 6 subjects (19.5%). Antimitochondrial antibody was positive in 4 patients. ANA was positive in one of these patients.

The distribution of histopathological findings by autoimmune hepatitis types is shown in Table 3. Human leucocyte antigenes A24,9, A26, A32, DRB1,15 were found with a higher rate in type-1. A26, B51, DRB1,11 were found with a higher rate in type-2. A32 and DRB1,04 were found with a higher rate in the undefined type.

In all subjects, deflazacort which is the oxazolinic derivative of prednisolone was started at a dose of 2 mg/kg/day (the highest dose: 60 mg/day). Response to treatment was evaluated every 4 weeks. According to serum ALT and AST levels and clinical status the dose of deflazacort was decreased by 2.5 or 5 mg every 6-8 weeks and a maintenance dose of 5 mg/day was reached. The mean time to reach the maintenance dose was 11 months. In 10 subjects in whom transaminases were found to be higher than 1,5 fold of the normal value at the end of the 3rd month, AZA was added at a dose of 1-2 mg/kg/day (the highest dose: 75mg/day). At the end of 2 years, 24 subjects (77.4%) were considered to have complete response, five subjects (16.1%) were considered to have partial response, 2 subjects (6.4%) were considered to have no response. These 2 subjects were lost to follow-up afterwards. At the end of the 3-year follow-up period, the dose of deflazacort was decreased up to 5 mg/every other day and the dose of AZA was decreased up to 5-10 mg/day in subjects with normal

Table 4. Complications which developed in our subjects after treatment

Complications	n (%)
Cataract	5 (16.1%)
Osteopenia	6 (19.35%)
Osteoporosis	4 (12.9%)

physical examination and laboratory findings. At the end of the 5-year follow-up period, treatment was ended in 6 (20.7%) subjects who had normal ALT and AST levels and normal histopathological examination of the liver. In one subject, the same treatment was started again, since the disease recurred 6 months later. 2 of the 5 subjects whose treatment was ended are being followed up for 6 years without any problem. 2 are being followed up for 5 years and 1 is being followed up for 4 years without any problem. In the second year, endoscopic examination was repeated, since thrombocyte count was lower than 150 000/mm^3, although liver enzymes were normal for a mean time of 82 months (48-96 months) in 5 of 23 subjects with a complete response and esophageal varices were found. However, variceal bleeding has not been observed in any subject, yet. The subjects are receiving the maintenance treatment without any problem. Hyperglycemia, hypertension or anemia related to AZA was not found in any of the subjects with a mean total follow-up time of 4.68±0.44 years (1-9 years). In 4 of all subjects, "cushingoid" appearance was observed in the first 3 months of deflazacort, but this appearance was eliminated as therapeutical dose was decreased. The weights and heights of the subjects were compatible with the age-appropriate curves. Cataract was found in 5 subjects, osteopenia was found in 6 subjects and osteoporosis was found in 4 subjects (Table 4). No other autoimmune disease was found on screening in our subjects.

Discussion

Although the reason of autoimmune hepatitis is not known exactly, it is thought that genetic predisposition and enviromental factors are involved in development of autoantibodies against hepatocytes. 80% of autoimmune hepatitis is type 1, 4% is type 2 and 3% is type 3 which is a rare type (2,3,5,8). The type in which autoantibodies can not be identified, but clinical and histological examination are compatible with AIH is called undefined AIH (11). Autoimmune hepatitis is observed more frequently in girls compared to boys (57-93%) and occurs most commonly at the ages of 10-20 years (mean 10 years of age) (11,17-19). We found female subjects with a rate of 64.5% and the mean age to be 12 years. The time between the age at the time of onset of the disease and the diagnosis was found to be 6 months in a study (20) and 8 months in 2 other studies (18,19). We found this time to be 10 months (2-25 months). Patients with autoimmune hepatitis present with acute or chronic signs. In North America and Europe, 26-40% of the subjects present with acute signs, while this rate is reported to be rather low in India (13.1%) (21). 82% of the pediatric subjects were reported to present with signs of acute hepatitis (22). Similar to the data of Gregorio et al. (17), 54,8% of our subjects presented with signs of acute hepatitis.

62-92% of the subjects with AIH were reported to be type 1 and 8-38% were reported to be type 2 in studies performed (17-19,23). 58% of our subjects were type 1 and 19.3% were type 2 which was compatible with the literature data. Autoimmune hepatitis type 1 is associated with positive ANA and/or SMA autoantibody. In Iranian children, positive ANA was found with a rate of 16.7-67%, positive SMA was found with a rate of 50-53% and positive ANA-SMA was found with a rate of 73.3% (19,23). Özen et al. (18) found positive ANA with a rate of 35,7%, positive SMA with a rate of 25% and positive ANA-SMA with a rate of 60%. In our study, we found positive ANA with a rate of 18.3%, positive SMA with a rate of 51,6% and positive ANA-SMA with a rate of 13%. Gregorio et al. (17) found the frequency of cirrhosis to be high in the subjects with positive ANA/SMA whom they followed up for 20 years. It was notable that three of our subjects who had severe fibrosis, but no cirrhosis were type 1. AMA positivity is usually associated with other autoantibodies in autoimmune hepatitis (24,26). We found positive LKM-1 in 2 of our 3 subjects with positive AMA and positive ANA in one. While LKM-1 antibody positivity is reported with a rate of 13-23% in the literature (19,23), we found LKM-1 to be positive in 6 (19.3%) of 31 subjects. As reported in the literature (17,18,26), the most common symptom at presentation was jaundice (71%) and the most common clinical findings were hepatomegaly (77.4%) and splenomegaly (54%) in our subjects. While 2-50 fold increases in transaminases are found in these patients, hypoalbuminemia has been reported with a rate of 20-50% (17,18,26). In our subjects, AST was found to be increased 50 fold and ALT was found to be increased 40 fold. Hypoalbuminemia was found with a rate of 35% and prolongation in prothrombin time was found with a rate of 42%. Autoimmune hepatitis is associated with autoinflammatory diseases with a rate of 22-50% (17,20). We found autoimmune hemolytic anemia in 2 of our subjects (7%) and familial Mediterranean fever in one. Viral infections including measles, EBV and hepatitis A and enviromental factors are blamed in addition to genetic factors in occurence of the disease (4,17,27,28). HAV IgM-IgG was positive in four of our subjects, EBV IgM was positive in six and we thought that these viral infections could be efficient in the occurrence of autoimmune hepatitis.

HLA DRB1,04 has been reported to be a significant risk factor in different studies (29-38). The frequency of A24,9, A26, A32, DRB1,15 was high in our type-1 subjects, the frequency of A26, B51, DRB1,11 was high in our type 2 subjects and the frequency of A32 and DRB1,04 was found high in the undefined type. The frequency of HLA DRB1,15 was similar to the data found in North Europe and America (39,40).

Currently, the treatment administered in autoimmune hepatitis includes prednisone alone or another immunosupressant drug like AZA in addition to prednisolone. Children in the growing period carry a risk in terms of toxic effects related to long-term steroid usage (41-45). Deflazacort is the oxazolinic derivative of prednisolone and has fewer side effects on glucose and bone metabolism. Since there are data indicating that deflazacort can be used because of fewer side effects and because of its efficiency in treatment, we used deflazacort in our subjects (44,45). We added AZA in 10 subjects who had no decrease in transaminases. At the end of two years, 77.4% of all subjects had complete response to treatment and 16% had partial response. 6.4% had no response. Although there ara few data about deflazacort, our results were found to be similar to the data in the literature (44,45). Even though liver enzymes are normal in the follow-up after treatment, is has been reported that severe hepatic decompensation can develop after years and liver transplantation may be required in 10% of the patients 10-15 years after the diagnosis (46). Gregorio et al. (17) reported that liver trasnplantation was performed approximately 5 years after the diagnosis in 8% of 97% subjects who received immunosuppresant drugs. Although transaminase levels were normal in 5 of our subjects with late response, the fact that marked fibrosis was found on histopathological examination of the liver after 7 years and presence of esophageal varices suggested that liver cirrhosis developed, but no variceal bleeding has been observed in any of these subjects.

It is known that early diagnosis and treatment of AIH in the pediatric age deccelerates progression to cirrhosis and prolongs survival. Since deflazacort used for treatment has few side effects and is efficient, we believe that it can be used in children with AIH. However, we think that more elucidative data will be obtained about the outcomes of the disease as the number of subjects with long-term follow-up increases.

Conflict of interest: None declared.

References

1. Oettinger R, Brunnberg A, Gerner P, Wintermeyer P, Jenke A, Wirth S. Clinical features and biochemical data of Caucasian children at diagnosis of autoimmune hepatitis. J Autoimmun 2005; 24: 79-84.
2. Mackay IR. Historical reflections on autoimmune hepatitis. World J Gastroenterol 2008; 14: 3292-300.
3. Vergani D, Mieli-Vergani G. Aetiopathogenesis of autoimmune hepatitis. World J Gastroenterol 2008; 14(21): 3306-12.
4. Czaja AJ. Autoimmune hepatitis: evolving concepts and treatment strategies. Dig Dis Sci 1995; 40: 435-56.
5. Z Ben-Ari, Czaja AJ. Autoimmune hepatitis and variant forms. Gut 2001; 49: 589-94.
6. Czaja AJ. Clinical features, differential diagnosis and treatment of autoimmune hepatitis in the elderly. Drugs Aging 2008; 25: 219-39.
7. Czaja AJ, Doherty DG, Donaldson PT. Genetic bases of autoimmune hepatitis. Dig Dis Sci 2002; 47: 2139-50.
8. Zachou K, Rigopoulou E, Dalekos GN. Autoantibodies and autoantigens in autoimmune hepatitis: important tools in clinical practice and to study pathogenesis of the disease. J Autoimmune Dis 2004; 15: 1-2.
9. Djilali-Saiah I, Fakhfakh A, Louafi H, Caillat-Zucman S, Debray D, Alvarez F. HLA class II influences humoral autoimmunity in patients with type 2 autoimmune hepatitis. J Hepatol 2006; 45: 844- 50.
10. Ma Y, Bogdanos DP, Hussain MJ, et al. Polyclonal T-cell responses to cytochrome P450IID6 are associated with disease activity in autoimmune hepatitis type 2. Gastro 2006; 130: 868-82.
11. Bellomo-Brandão MA, Costa-Pinto EA, De Tommaso AM, Hessel G. Clinical and biochemical features of autoimmune hepatitis in 36 pediatric patients. Arq Gastroenterol 2006; 43: 45-9.
12. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999; 31: 929-38.
13. Czaja AJ. Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. Hepatology 2008; 48: 1540-8.
14. Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981; 1: 431-5.
15. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994; 19: 1513-20.
16. Fallatah HI, Akbar HO, Qari YA. Autoimmune hepatitis: single-center experience of clinical presentation, response to treatment and prognosis in Saudi Arabia. Saudi J Gastroenterol 2010; 16: 95-9.
17. Gregorio GV, Portmann B, Reid F, et al. Autoimmune hepatitis in childhood: a 20-year experience. Hepatology 1997; 25: 541-7.
18. Ozen H, Koçak N, Saltik IN, Yüce A, Gürakan F. Autoimmune hepatitis. Indian J Pediatr 2001; 68: 725-8.
19. Rafeey M, Kianrad M, Hasani A. Autoimmune hepatitis in Iranian children. Indian J Gastroenterol 2007; 26: 11-3.
20. Maggiore G, Veber F, Bernard O, et al. Autoimmune hepatitis associated with anti-actin antibodies in children and adolescents. J Pediatr Gastroenterol Nutr 1993; 17: 376-81.
21. Choudhuri G, Somani SK, Baba CS, Alexander G. Autoimmune hepatitis in India: profile of an uncommon disease. BMC Gastroenterol 2005; 5: 27.
22. Porta G, Miura IK, Cardoso RA, et al. Clinical and laboratory features of Brazilian children with autoimmune hepatitis types 1 and 2. J Pediatr Gastroenterol Nutr 2000; 31(2): 4.
23. Najafi M, Kianifar HR, Mir-Nasseri SMM, et al. Autoimmune hepatitis in children, clinical features and biochemical of Iranian children. Govaresh 2005; 10: 103-7.
24. Gregorio GV, Portmann B, Mowat AP, Vergani D, Mieli-Vergani G. A 12-year-old girl with antimitochondrial antibody positive autoimmune hepatitis. J Hepatol 1997; 27: 751-4.
25. Kenny RP, Czaja AJ, Ludwig J, Dickson ER. Frequency and significance of antimitocondrial antibody in severe chronic active hepatitis. Dig Dis Sci 1986; 31: 705-11.
26. Özsoylu S, Yüce A, Koçak N. Çocuklarda kronik aktif hepatitler: 47 vakanın analizi. (Chronic active hepatitis in children: analysis of 47 cases). Turk J Gastroenterohepatol 1993; 4: 33-6.
27. Vento S, Garofano T, Di Perri G, Dolci L, Concia E, Bassetti D. Identification of hepatitis A virus as a trigger for autoimmune chronic hepatitis type 1 in susceptible individuals. Lancet 1991; 337: 1183-7.
28. Urganci N, Akyildiz B, Yildirmak Y, Ozbay G. A case of autoimmune hepatitis and autoimmune hemolytic anemia following hepatitis A infection. Turk J Gastroenterol 2003; 14(3): 204-7.
29. Pando M, Larriba J, Fernandez GC, et al. Pediatric and adult forms of type I autoimmune hepatitis in Argentina: evidence for differential genetic predisposition. Hepatology 1999; 30: 1374-80.
30. Duarte-Rey C, Pardo AL, Rodríguez-Velosa Y, Mantilla RD, Anaya JM, Rojas-Villarraga A. HLA class II association with autoimmune hepatitis in Latin America: a meta-analysis. Autoimmun Rev 2009; 8: 325-31.
31. Teufel A, Wörns M, Weinmann A, et al. Genetic association of autoimmune hepatitis and human leucocyte antigen in German patients. World J Gastroenterol 2006; 12: 5513-6.
32. Muratori P, Muratori L, Pappas G, et al. Genetic distinctions between autoimmune hepatitis in Italy and North America. World J Gastroenterol 2005; 11: 1862-6.
33. Umemura T, Ota M, Yoshizawa K, et al. Lack of association between FCRL3 and FcgammaRII polymorphisms in Japanese type 1 autoimmune hepatitis. Clin Immunol 2007; 122: 338-42.

34. Yokosawa S, Yoshizawa K, Ota M, et al. A genomewide DNA microsatellite association study of Japanese patients with autoimmune hepatitis type1. Hepatology 2007; 45: 384-90.
35. Yoshizawa K, Ota M, Katsuyama Y, et al. Genetic analysis of the HLA region of Japanese patients with type 1 autoimmune hepatitis. J Hepatol 2005; 42: 578-84.
36. Ma X, Qiu DK. Relationship between autoimmune hepatitis and HLA-DR4 and DRβ allelic sequences in the third hypervariable region in Chinese. World J Gastroenterol 2001; 7: 718-21.
37. Qiu DK, Ma X. Relationship between type I autoimmune hepatitis and alleles of HLA-DRB1 in Chinese patients of Shanghai area. Zhonghua Gan Zang Bing Za Zhi 2002; 10: 347-9.
38. Qiu DK, Ma X. Relationship between human leukocyte antigen-drb1 and autoimmune hepatitis type I in Chinese patients. J Gastroenterol Hepatol 2003; 18: 63-7.
39. Czaja AJ, Strettell MD, Thomson LJ, et al. Associations between alleles of the major histocompatibility complex and type1 autoimmune hepatitis. Hepatology 1997; 25: 317-23.
40. Strettell MD, Donaldson PT, Thomson LJ, et al. Allelic basis for HLA-encoded susceptibility to type 1 autoimmune hepatitis. Gastroenterology 1997; 112: 2028-35.
41. Heneghan MA, McFarlane IG. Current and novel immunosuppressive therapy for autoimmune hepatitis. Hepatology 2002; 35: 7-13.
42. Roberts EA. Autoimmune hepatitis. Indian J Pediatr 1995; 62: 525-31.
43. Alvarez F, Ciocca M, Canero-Velasco C, et al. Short-term cyclosporine induces a remission of autoimmune hepatitis in children. J Hepatol 1999; 30: 222-7.
44. Bae SH, Kim JS, Kim DH. Deflazacort for type-1 autoimmune hepatitis in a Korean girl. J Korean Med Sci 2006; 21: 758-60.
45. Bernardez RJ, Mimoso CC, Moreno PA, et al. Deflazocort for long-term maintenance of remission in type 1 autoimmune hepatitis. Rev Esp Enferm Dig 1999; 91: 630-8.
46. Mieli-Vergani G, Vergani D. Autoimmune paediatric liver disease. World J Gastroenterol 2008; 14(21): 3360-7.