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# Characteristics and Outcome of three forms of Autoimmune Hepatitis in Iranian Children

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***Abstract***

***Introduction***
To define the clinical features, biochemical and histological findings and outcome of three forms of autoimmune hepatitis.

***Materials and Methods***
In a cross sectional study between November 2001 to January 2008 in Tehran and Mashhad university of medical sciences, 61 children who diagnosed as AIH (40 girls and 21 boys) have been analyzed for their clinical, serological, and histological data. Variables analyzed included age, sex, clinical presentation, hepatic function, immunoglobulins, autoimmunity markers, histology and clinical evolution. According to the auto-antibodies profile, AIH patients were classified as type I AIH (ANA or smooth-muscle antibodies or both positive), type II (anti-LKM-1 positive) and type III (antibody negative).

***Results***
We analyzed data of 61 children with AIH. 51 patients (median age: 10 (0.7-14) years had anti-nuclear and/or smooth muscle antibody (ANA/ASMA or both), 5 (median age: 7 (2-8) years) had liver/kidney microsomal antibody (LKM-1). 5 patients had no detectable autoantibody. At presentation: 60% had jaundice or symptoms of acute hepatitis; LKM-1 positive were younger. Interface hepatitis was seen in 100% and fibrosis+/- cirrhosis were found in 70%. Frequency of AIH was 2:1 in girls. Type 1 was the most frequent diagnosis (83%) and was more frequent in older children. Relapse and treatment failure were common in type II.

***Conclusion***
AIH may have different clinical presentation in children. Althout most of cases may have high inflammatory activity or cirrhosis, good response to treatment and remission may accur.

***Keywords***
Autoimmune hepatitis, Type 1, Type 2; Child.

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## Introduction

Autoimmune hepatitis (AIH) is believed to be an inflammatory liver disease that is histologically defined by a dense mononuclear cell infiltrate, such as plasma cells and macrophages located in the portal tract. Serologically, the presence of autoantibodies and increased immune-globulin G (IgG) are hall mark of the disease (1,2). The onset of these conditions is often ill-defined, frequently mimicking acute hepatitis. Numbers of publications on AIH in children are limited and therefore more cases and researches needed to define its presentation and course in childhood. We aimed to define clinical and laboratory characteristics as well as outcome of it in the pediatric age group.

## Materials and Methods

Between 2001 to 2008, in a cross sectional study, 61 children with the diagnosis of autoimmune hepatitis in Children Medical Center Hospital of Tehran and Mashhad University of Medical Sciences enrolled in the study. Levels of aspartate amino-transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (AP), albumin, gamma-globulin and International Normalized Prothrombin ratio (INR) were determined. To rule out other diagnosis, hepatitis B surface antigen, hepatitis C antibody, HCV DNA, complete work- up for Wilson's disease and alpha-1-antitrypsin deficiency were done. None of these cases had a history of blood transfusion, surgery or intake of hepatotoxic drugs. HAV IgM test was done for patients who were presented as acute hepatitis.

Autoimmune markers ANA, ASMA and anti- KLM-1 were tested by using indirect immunofluorescence in all cases. If it was possible, liver biosy was done.

Autoimmune liver disease was diagnosed when one or more of the autoantibodies (ANA, A SMA titers>1/20, and anti LKM-1 titer>1/10 were positive). 3 We applied the criteria to define AIH and response to the treatment of the patients.4 By using a questionnaire, data on demographic clinical & biochemical findings were collected. Patients were treated with prednisolon 2 mg/kg per day (maximum 60 mg /d). This was gradually tapered by 5-10 mg every 2 weeks depending on symptoms and AST activity. Prednisolon was decreased to the lowest possible maintenance dose (usually 5 mg /day). Azathioprin (1-2 mg /kg /d)was added if AST level increased on reducing the corticosteroid dose, or if corticosteroid side –effect necessitated a reduction in its dose. In refractory cases cyclosporine (4-6 mg/Kg) was used. Statistical analysis was performed with SPSS 11.5. Univariate analysis was performed with the exact test and kruskalwalis test.

Patients and their parents gave their informed consent. This study was approved by local ethics committee.

## Results

40 out of 61 patient with autoimmune hepatitis were female and 21 were male,aging from 7 months to 14 years (mean age 8 years). 51 out of 61 were diagnosed as having type 1 AIH, 5 had AIH type 2 and 5 had cryptogenis chronic hepatitis (type 3). The patients had not a history of blood transfusion, surgery or intake of hepatotoxic drugs. As presentation, icter and signs of chronic liver disease were found in 36 (60%), and it was the most aboundant finding. Abnormal liver function test that was detected in routine check up was the presenting symptom in 7 (11.6%). We revealed clubbing in 12 (20%), ascitis in 9 (15%), hepatosplenomegaly in 9(15%), GI bleeding in 3(5%), failure to thrive in 4(6.6%) and constitutional symptom such as anorexia, fatigue or weight loss in 2(3.2%). Our patients had not fulminant hepatitis or encephalopathy as a chief complaint. In table 1 clinical data are shown.

**Table 1:** clinical characteristics of three forms of AIH.

| | Type of hepatitis | | | |
|---|---|---|---|---|
| | I | II | III | P Value |
| Gender,female/male | 34/17 | 5/0 | 1/4 | 0.06 |
| Median age at diagnosis | 10 | 7 | 5 | 0.013 |
| Clinical features Icter | 30(58%) | 4(80%) | 2(40%)) | 0.59 |
| epatosplenomegaly | 7(13%) | 1(20%) | 1(20%) | 0.78 |
| GI bleeding | 3(5.8%) | 1(20%) | 0 | 0.41 |
| Abnormal LFT | 7(11.6%) | 0 | 2(40%) | 0.35 |
| Constitutional | 3(5.8%) | 0 | 0 | 0.75 |
| FTT | 2(4%) | 0 | 2(40%) | 0.01 |
| Clubbing | 10(19%) | 2(40% | 0 | 0.32 |
| Ascites | 6(11.7%) | 3(60%) | 0 | 0.01 |

Anti-nuclear antibodies, anti-smooth muscle antibodies corresponding to AIH type 1 were detected in 51 children (34 girls, 17 boys, 2:1). SMA was exclusively present in 40 children (66%), ANA in 7 (11.5%). Only 2 (3.2%) had positive SMA and ANA simultaneously. Anti-liver kidney microsomal antibodies characterizing AIH type 2 were detected in 5 patients (8.1%) which all of them were female. In 5 children (8.1%) no autoimmune antibodies could be identified despite characteristic clinical and histological findings and response to corticoestroid. The laboratory findings were non significant between three forms of AIH. Data are shown in (Table 2).

**Table 2:** Laboratory findings in AIH type I,type II and type III.

| Type of hepatitis<br>Biochemical markers | AIH I | AIH II | AIH III | Total | P value |
|---|---|---|---|---|---|
| ALT(U/l)<br>(mean +sd) | 546 (563)* | 482<br>(478) | 243<br>(196) | 522<br>(540) | 0.660 |
| AST (U/l)<br>(mean +sd) | 654<br>(615) | 530<br>(516) | 260<br>(105) | 618<br>(591) | .494 |
| T.billi(mg/dl))<br>(mean +sd) | 6.9<br>(6.7) | 5.5<br>(2.9) | 3.4<br>(2.6) | 6.5<br>(6.1) | .504 |
| D.billi(mg/dl)<br>(mean +sd) | 4.1<br>(4.4) | 3.3<br>(2.1) | 2.2<br>(1.7) | 3.8<br>(4.1) | .594 |
| PT (sec)<br>(mean +sd) | 16.1<br>(3.7) | 18.2<br>(4.6) | 14<br>(1.2) | 16.1<br>(3.7) | .239 |
| T.protein(G/L))<br>(mean +sd) | 7.7<br>(2.9) | 7.6<br>(.66) | 7<br>(.45) | 7.6<br>(1.1) | .580 |
| Globulin (G/L)<br>(mean +sd) | 3.7<br>(1.1) | 3.7<br>(.34) | 3.1<br>(.13) | 3.7<br>(1) | .420 |
| Alk (U/l)<br>(mean +sd) | 743<br>(353) | 991<br>(120) | 738<br>(500) | 761<br>(358) | .394 |
| Hgb (mg/dl)<br>(mean +sd) | 10.3<br>(1.9) | 10.1<br>(2) | 11.8<br>(1.1) | 10.4<br>(1.9) | .431 |
| Plt(nl)<br>(mean +sd) | 156<br>(88) | 255<br>(160) | 183<br>(423) | 167<br>(96) | .083 |

*Mean (standard deviation)

Histological exploration of 43 children revealed mean of 7.5(2-11) for HAI grading and 4.1(0-6) for stage. 100% and 70% of patients had interface hepatitis &fibrosis+/-cirrhosis, respectively .Data of histological scoring in each type of disease are shown in (Table 3).

**Table 3:** Histological staging and grading of types of AIH.

| Severity type of hepatitis | Grade Mean(SD) | Stage Mean(SD) |
|---|---|---|
| AIH I | 7.6(3.8) | 4.2(1.6) |
| AIH II | 7.7(4.1) | 4.7(1) |
| AIH III | 5.2(2.8) | 3.7(2.6) |
| Total | 7.5(3.7) | 4.1(1.7) |
| P value | 0.73 | 0.43 |

Various side effects like osteoporosis, cushingoid facies were observed in some children on steroid therapy. Also we detected hypertricosis and gingival hyperplasia in children who were on cyclosporine therapy.

The results of response to the treatment were shown in (Table 4).

**Table 4:** Response to immunosuppressant treatment in patients with AIH

| | Type of hepatitis | | | |
|---|---|---|---|---|
| | I | II | III | |
| No response | 3* (5.8%) | 0 0% | 0 0% | 3 (5%) |
| Biochemical remission | 41 (80.3%) | 2 (40%) | 4 (80%) | 47 (77%) |
| Histological remission | 3 (5.8%) | 0 0% | 0 0% | 3 (5%) |
| Treatment failure | 2 (3.9%) | 1 (20%) | 0 0% | 3 (5%) |
| Relapse | 2 (3.9%) | 2 (40%) | 1 (25%) | 5 (8%) |
| Total | 51 | 5 | 5 | 61 |

*No.(Percent)

## Discussion

Autoimmune hepatitis can be presented commonly as an acute hepatitis in children.5 In western countries it seems to be cause of 20% of chronic hepatitis 6 and it is reporeted as 3.9% of chronic liver disease in India.7 Autoimmune hepatitis has been described to have a female preponderance(1,5-8). This ratio is about 4:1 in some reports and almost equally distributed frequency in the United states (1,8-10). In our study the overall female/male ratio was 2:1. Disease predominance in female is depending on the type of of AIH, we also revealed in our study that all of 5 patients with type 2 were female.

The disease was spread over all age groups with slight peaks at 7, 11 to 14 years. Patients with type 2 seem to be younger with higher bilirubin levels and a higher inflammatory activity (Grading in liver biopsy). In Porta et al study children with type 1 AIH were older at onset (mean age 8 vs. 3 years) and Gregorio et al study reported a mean age of 10 years for type 1 and 7 years for type 2 and in Oettinger etal study also mean age of 11.5 years versus 9 years reported for type 1 and 2, respectively (9,11,12). In our patients type 1 showed an increasing frequency with age whereas the incidence of type 2 was independent of age.

The clinical picture of AIH is characterized by a wide spectrum of symptoms: from mild to severe, with or without extrahepatic manifestations. AIH in children in 50-65% is characterized by a sudden onset and clinical symptoms similar to those of acute viral hepatitis (5,13,14). The disease can be typically presented as fluctuating jaundice, weakness, anorexia and abdominal pain as usual features, but a significant group of these patients have no obvious signs or symptoms of liver disease at all.8,9 36 of our patients presented as acute hepatitis or jaundice that was the most frequent symptom in our study (60%). In independent studies 60%, 63% , 56% and 57.7% of reported patients had jaundice at

presentation8,9,11,13 In the Porta et .al report the majority (82%) had symptoms of acute hepatitis at presentation 15 We also detected more ascites in type II and poor weight gain in type III of our patients. If AIH remains untreated, progression to liver cirrhosis with consequent liver failure is usually inevitable (5,16,17). Standard treatment of AIH is corticosteroid with or without azathioprine and it can be effective in the remission induction. 5,12,16-18 With this method of therapy, 65% of patients can achieve remission within 18 months and 80% within three years. Serum transaminase activity can normalize about 6 mo in type I and 9 mo in type II.20 Relapse may occur in about 40% of the patients who are treating and it forces to increase steroid dose. Treatment failure with clinical, laboratory and histological progression despite adherence to therapy occurs in up to 10% of patients.5 Non-adherence, particularly in adolescents, is important reason of relapse. However, when treatment are countinued to achieve normal serum AST, gamma-globulin, and serum IgG levels , a lower frequency of relapse will expectable and vice versa (17,19-21). Ten years of follow-up showed that near 10% of children with autoimmune hepatitis will die.5.

Over than 80% of our patients had remission (biochemical or histologic) on standard therapy, which it was more frequently seen in type I (86%) and least in type II(40%). We also revealed that relaps and treatment failure was more common in AIH type II. It is clear that true remission is hard to achieve. Immunosuppressive therapy can not cure autoimmune disease because it does not treat the underlying factors of the disease. Thus, the aim of therapy will be normalization of laboratory tests in AIH. 22 We believe that treatment duration may be one of the important factors in reducing the relapse rate in AIH.

Our data showed, AIH type 1 was the predominant form of autoimmune hepatitis in our children. The number of patients diagnosed increase with age, particularly in type 1. Boys were affected half as much as girls by type 1. Jaundice is the most common presentation of disease, which seen in acute hepatitis, Therefore autoimmune liver disease should be considered as a differential diagnosis.

Early diagnosis and treatment of disease may decrease clinical and histological features of cirrhosis and could prolong the survey.

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