Original Article

Autoimmune hepatitis in Iranian children

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Objective: To evaluate the clinical and para-clinical presentation, including autoantibody pattern, and response to treatment in Iranian children with autoimmune hepatitis (AIH). **Methods:** Data of 60 children presenting with AIH (56 girls) were analyzed retrospectively for clinical, serological and histological profile. **Results:** Clinical findings included jaundice (67%),hepatomegaly (50%) and ascites (30%). Forty children (38 girls) had type I AIH and 14 (12 girls) had type II AIH. Liver histology was comparable in the two groups and cirrhosis on initial biopsy was equally frequent in Types I and II AIH (63% *vs* 34%; p=ns). **Conclusion:** Our study describes the presentation and clinical course of Iranian children with AIH. Treatment with corticosteroids and/or azathioprine induces remission of autoimmune hepatitis clinically, biochemically as well as histologically. [*Indian J Gastroenterol* 2007;26:11-13]

In children, autoimmune hepatitis (AIH) presents most commonly as an acute "hepatitis-like syndrome" (50%-73%); however, acute liver failure has been reported in 10% of cases.[1,2] The International Autoimmune Hepatitis Group has drawn up guidelines for making the diagnosis of AIH based on clinical and biochemical criteria. The sensitivity of these criteria ranges from 97% to 100% and specificity is at least 89.8%.[3,4,5]

AIH is a well documented entity in the West but not much literature is available on this subject from the Middle East.

Methods

Between 1999 and 2004, the Division of Gastroenterology at our tertiary hospital investigated 1071 patients with acute or chronic liver disease. Of these, 60 patients (5.6%) fulfilled the criteria for either definite (n=54) or probable (n=6) AIH, as per the revised scoring system proposed by the International Autoimmune Hepatitis Group.[1,3,4]

Autoantibody tests (*Euro test*, UK) included immunofluorescence for anti-smooth muscle antibody (ASMA) and antinuclear antibodies (ANA), and enzyme immunoassays for anti-liver/kidney microsomal antibody (anti-LKM) and anti-mitochondrial antibodies (AMA). For anti-LKM and AMA, titers exceeding 5 U/L and for ANA and ASMA $\geq$20 U/L were taken as positive. Serum markers for hepatitis A, B, C and E, and serum ferritin, serum ceruloplasmin, alpha-l antitrypsin were tested to exclude viral and metabolic causes of liver disease. Percutaneous needle liver biopsy was done if the clinical and laboratory background permitted.

AIH was subdivided into: Type 1, characterized by ANA and/or ASMA; and Type 2, characterized by anti-LKM_1 antibodies. We did not test for antibodies to soluble liver antigen and liver-pancreas antigen.

Patients who had elevated transaminases (more than five times upper normal limit [0-40 IU/L]), hypergammaglobulinemia (more than twice normal [2-3.5 g/dL]) and disease activity on histology were treated with prednisolone 2 mg/Kg/d (maximum 60 mg/d).[6] This was gradually tapered by 5-10 mg every 2 weeks depending on symptoms and AST activity. Prednisolone was decreased to the lowest possible maintenance dose (usually 5 mg/day). Azathioprine (1-2 mg/Kg/d) was added if AST level increased on reducing the corticosteroid dose, or if corticosteroid side-effects necessitated a reduction in its dose.

Remission was defined as absence of clinical symptoms and normal AST level (<50 IU/L) on two occasions at least one month apart. Relapse was defined as at least two-fold increase in AST levels (>100 IU/L), with or without recurrence of symptoms. On relapse, prednisolone (1-2 mg/Kg/d) treatment was re-instituted and gradually tapered.

Discontinuation of immunosuppressive treatment (azathioprine and/or corticosteroids) was considered when aminotransferase levels measured at 3-month intervals were normal for at least 1 year and repeat liver biopsy showed absence of necro-inflammatory activity.

Statistical analysis was done using SPSS software with independent *t* test. The study was approved by the Institutional Review Board of the Faculty of Medical Sciences.

Results

The 60 patients (56 girls) had a median age of 8.4 (range 3-13) years. The median duration of symptoms was 8 months. Approximately all of the patients had good nutritional status at the time of diagnosis. Weight and height of patients were measured during the first visit prior to treatment. Reference tables from the National Center of Health Statistics were used as reference value.[7] Fifty (83%) patients presented as chronic liver disease, two (3%) with fulminant hepatic failure, and 8 (13%) as acute liver disease.

Physical examination revealed jaundice in 40 (67%) patients, hepatomegaly in 30 (50%), and ascites in 18 (30%) patients; 6 (10%) patients had history of gastrointestinal bleed. The laboratory parameters are listed in Table 1. ANA were positive in 40 (67%) patients and ASMA in 32 (53%); anti-LKM_1 was positive in 14 (23%) patients. Forty (38 girls) patients had Type 1 AIH and 14 (12 girls) had Type 2 AIH. As per the revised scoring system, 54 (90%) patients had definite AIH and the rest had probable AIH.[4,8,9] AMA was positive in 8 of 56 patients tested. Other antibodies included rheumatoid factor (4 patients), double-stranded DNA (dsDNA) antibodies (4), anti-microsomal antibody (2), and anti-thyroglobulin (2). Thirteen patients had associated illnesses (Table 2).

Fifty patients underwent liver biopsy before treatment. In 4 patients, biopsy was possible only 6 months after starting immunosuppressive treatment when the coagulation tests had become normal. Fifty follow-up liver biopsy specimens were obtained 1-3 years after the diagnosis; in the remaining 10 patients, it was not done either because of deranged coagulation parameters or lack of parental consent.

Table 1: Liver biochemistry

Investigation	Value	No. of patients (%)
Elevated bilirubin	0-1	20 (33.3%)
(N 0.2-1.0 mg/dL)	2-5	10 (16.6%)
	5-10	4 (6.7%)
	>10	26 (43%)
ALT, AST*	<5	18 (30%)
(N 0-40 IU/L)	>5	42 (70%)
Alkaline phosphatase (N 0-180 IU/L)	Elevated	24 (40%)
Globulins (N 2.0-3.5 g/dL)	>3.5	46 (76.6%)

*times upper limit of normal range

Table 2: Clinical features at presentation (6 patients unclassified and not recorded)

Clinical presentation	ANA/ASMA positive (n=40)	LKM-1 positive (n=14)
Age at diagnosis (y), median	9	6
Female n (%)	38	12
Fulminant liver failure n (%)	2	2
Associated autoimmune disorder		
Autoimmune thyroiditis	2	1
Ulcerative colitis	2	0
Systemic lupus erythematosis	4	0
Insulin-dependent diabetes	2	0
Vitiligo and alopecia	0	2

In 4 patients who tested positive for ANA, ASMA, AMA and anti-neutrophilic cytoplasmic antibody, serum alkaline phosphatase and gamma glutamyl transpeptidase levels were markedly elevated. Liver biopsy revealed hepatitis around the portal triad and onion-skin pattern of duct obliteration. Endoscopic retrograde cholangiography was not done. Magnetic resonance cholongiography revealed focal irregularity of the right and left hepatic ducts, representing strictures, suggesting primary sclerosing cholangitis (PSC); these children were diagnosed to have PSC/AIH overlap syndrome.

In the remaining 56 patients, the severity of portal tract inflammation, lobular activity and periportal activity was similar in patients with Type 1 and Type 2 disease. The proportion of patients with liver cirrhosis on initial biopsy was also similar in the two types of disease (63% *vs* 48%; p=ns).[6]

Repeat liver biopsy done in 50 patients showed decreased inflammation in 36 and no change or worsening of inflammation in 14 patients. At 1-6 months after starting corticosteroid treatment, a 75% reduction in the AST and INR and normal serum albumin level was observed in 40 patients. Of 56 patients with abnormal baseline bilirubin levels, these returned to normal in 20 patients, 1-20 months after the start of treatment. Fifty-five patients had good primary response to treatment. In 2 patients, after complete remission as observed on liver biopsy and six to eight months after tapered immunosuppressive therapy, the disorder relapsed and azathioprine or prednisolone was administered again. Two patients died during the study, one of fulminant hepatic failure and another of disease flare due to discontinuation of drugs while waiting for transplantation.

Discussion

Children with AIH present distinct clinical features and outcome compared to adults.

In our hospital, a referral center for northwestern part of Iran, AIH formed 5.6% of all childhood liver disease. In studies from India, AIH accounted for 3.5%-6.1% of chronic liver disease,[10-13] which is lower than the 11%-23% frequency reported in North America and Western Europe,[14] but similar to that (5%-10%) in Brazil.[15] However, AIH is not uncommon in Iran as in other developing countries.[10,15,16]

The prevalence, female preponderance, clinical features, extrahepatic manifestations and predominance of type 1 AIH in our series are similar to those in the other studies in Brazil and Europe.[15,17] The median period between onset of symptoms and diagnosis was 8 months in our study, but Gregorio reported a shorter interval (1-1.8 mo).[17] Using the scoring system proposed by the International Autoimmune Hepatitis Group, 90% of the children fulfilled the criteria for the diagnosis of definite AIH before treatment, suggesting that the scoring system, derived from the analysis of adult patients, may also be applicable in the pediatric age group.[4,8,9]

Our patients showed good response to immunosuppressive drugs, comparable to data in the Western literature.[9,17] The encouraging results recently reported with the use of cyclosporine A in children with AIH should therefore be evaluated on the a large number of patients from different centers.[18]

Although Gregorio and coworkers showed sclerosing cholangitis and AIH are similarly prevalent in childhood, in our study, autoimmune sclerosing cholangitis was rarely observed.[17,19]

In summary, AIH accounted for 5.6% of patients being referred with liver disease at our center. A majority had chronic liver disease and type 1 AIH. There was good response to immunosuppressive therapy.

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Received June 14, 2006. Received in final revised form October 30, 2006. Accepted November 5, 2006