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Survey of Autoimmune Hepatitis in Children

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Abstract: Autoimmune Hepatitis (AIH) is a disease of unknown etiology. The incidence rate of AIH in European countries amounts to 0.69 per 100,000 of the population per year. Autoimmune Hepatitis (AIH) is an unresolving hepatocellular inflammation of unknown cause that is characterized by presence of periportal hepatitis on histological examination, tissue antibodies in serum and hypergammaglobulinemia. To study the clinical profile, response to treatment and complication in Iranian children with AIH, that admitted in division of gastroenterology/hepatology, children Hospital of Tabriz University of medical sciences. In descriptive and cross-sectional study, 30 patients with autoimmune hepatitis that admitted in the pediatric hospital from 1997 to 2007 selected and necessary information such as age, sex, clinical signs and symptoms and methods of treatment collected from patients records and evaluated. The descriptive findings were reported as percent of frequency and mean. They followed for three years. Autoimmune hepatitis constituted 5.6% of chronic hepatitis cases. Of 30 children, 28 were girls and 2 were boys. Mean age of patients was 8.4 years (range 3-13 years). The most common type of autoimmune hepatitis was type 1 with 17 patients. Immunosuppressive therapy with prednisolon and Azathioprine was the most common treatment in the patients. Jaundice was the most common presentation symptom of patients with 27 patients. In most patients there was suitable response to immunosuppressive therapy. One patient died and five of them are waiting for liver transplantation. Type I autoimmune hepatitis was the predominant type of autoimmune hepatitis in children. The majority of patients with autoimmune hepatitis presented with liver signs such as jaundice, hepatomegaly and paraclinic findings such as impairment of liver function test. Autoimmune hepatitis was female predominant disease. There was suitable response to immunosuppressive therapy.

Key words: Autoimmune hepatitis, treatment, children, ATH, patient

INTRODUCTION

Definition: Autoimmune Hepatitis (AIH) is a disease of unknown etiology that follows a chronic but fluctuating course during which a progressive destruction of the hepatic parenchyma occurs. AIH often shows a good response to immunosuppressive treatment. Two types of AIH are currently recognized according to the nature of the autoantibody detected in children, sera at the time of diagnosis. Type 1 AIH is characterized by the presence of Anti-Smooth Muscle Antibodies (ASMA) and/or Anti-Nuclear Antibodies (ANA), type 2 AIH by anti-Liver-Kidney Microsome (LKM) and/or anti-Liver Cytosol (LC1) antibodies (Johnson and McFarlane, 1993).

The incidence rate of AIH: The incidence rate of AIH in European countries amounts to 0.69 per 100,000 of the population (Baranov *et al*., 2003),with the morbidity much higher amongst the Caucasians. Within the structure of chronic hepatic diseases, AIH in adults is known to account for 10-20% (Manns, 1996). The prevalence of AIH in children has not been determined as yet. Findings show that the prevalence of the disease in pediatric practice is low (Manns, 1996).

Etiology and pathogenesis of AIH: The etiology of AIH is unknown and its pathogenesis has so far been studied insufficiently. There are some ideas about the role of Epstein-Barr virus (Vento *et al*., 1995), measles (Maggiore *et al*., 1993), hepatitis A and C viruses (Rahaman *et al*., 1994; Simonovic *et al*., 1999), as well as drugs (interferon) (Gareia-Buey *et al*., 1995), as possible triggering factors of the disease. One cannot exclude the possibility that AIH develops after the primarily determined immune response disorder, when the appearance of the improhibited clones of autoreactive cells takes place without the influence of the trigger factors (Czaja, 1995).

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Classification of AIH: Type 1 AIH is characterized by the presence of Antinuclear Antibodies (ANA) and/or Anti Smooth Muscle Antibodies (ASMA) in the blood serum in the titr 1:80 in adults and 1:20 in children, This type, representing the classical variant of the disease, accounts for about 80% of all the AIH cases. Type 1 AIH is diagnosed at any age, but usually from 10-20 or from 45-70 years (Czaja, 1998).

Type 2 AIH patients have anti-LKM $_1$ antibodies in serum. Type 2 AIH accounts for approximately 3% (Sherlock, 1994; Czaja *et al*., 2000; Tyurina *et al*., 1999) of all the cases of AIH. The majority of the patients are children 2-14 years old (Johnson *et al*., 1993).

Some authors single out type 3 AIH which is characterized by the presence of antibodies to a soluble liver antigen (anti-SLA), but the absence of ANA or anti-LKM. Patients with type 3 AIH often reveal ASMA(35%), mitochondrial antibodies (22%), rheumatoid factor (22%) and antibodies to liver-membrane antigen anti-LMA (26%) (Johnson *et al*., 1993).

The aim of this was survey of autoimmune hepatitis in children with liver disease.

MATERIALS AND METHODS

Between 1997-2007, in the pediatric hospital of Tabriz 30 patients diagnosed as having AIH are presented. In a cross-section and descriptive study, we selected 30 patients with AIH.

Necessary information such as symptoms of patients including: Jaundice, splenomegaly, hepatomegaly, anorexia, epistaxis and fatigue, ascites, abdominal pain, fever, vomiting, GI bleeding, hypertension, acholic stool, dark urine, hematemesis, palmar erythema, cyanosis, Spider angioma and edema, antibodies finding and received treatment collected . The descriptive findings were reported as percent of frequency and mean. They followed for 3 years. Liver functional test and PT, PTT were checked every 2 weeks and then monthly.

Diagnosis was based on routine biochemical and immunologic analysis, histopathology of the liver and exclusion of viral and metabolic etiologies. Drug consumption or exposures to toxic agents were excluded in all patients. Hepatitis B, hepatitis C, epstein-barr and cytomegal viruses were excluded by appropriate serologic markers. Wilson's disease was excluded in all by normal serum ceruloplasmin and normal 24 h urinary copper excretion as well as negative copper staining and normal hepatic copper concentration in liver biopsies. Alpha-1 antitrypsin concentrations were within normal limits in all patients. Alanine Aminotransferase (ALT) was measured by the hospital laboratory. Antinuclear Antigen (ANA), Smooth Muscle Antibody (ASMA) and Liver-Kidney-Microsomal antibody (LKM-1) and AMA (antimitochondrial antibody) were tested at a dilution of 1:10 in phosphate-buffered saline by indirect immunofluorescence.

Treatment: After the diagnosis, all patients were put on prednisolone treatment at a dose of 1-2 mg/kg/day (maximum 60 mg day^{-1}). This dose was gradually tapered by 5 mg every week after the first week of therapy until the maintenance dose of 15 mg/day was achieved. Azathioprine (1-2 mg/kg/day) was added to steroid therapy in 27 patients because the dosage of steroid had to be reduced due to significant side effects such as glucose intolerance (in two) and hypertension (in one). In 27 patients Azathioprine was used temporarily due to the development of cataract. No other immunosuppressant was used.

AIH was subdivided into: Type 1, characterized by antinuclear antibodies and/or anti-smooth muscle antibodies; type 2, characterized by anti-LKM1 antibodies.

RESULTS

Of the 30 children, 28(93.3%) were girls and 2(6.7%) were boys, mean age 8.4±2.4 years (range 3-13 years).

Symptoms and signs of patients

At first: The symptoms and signs were as follows: jaundice in 28 (1 male), splenomegaly 22 (2 males), hepatomegaly in 15 (2 males), anorexia, epistaxis and fatigue in 13, ascites in 9, abdominal pain and fever in 8, dark urine and acholic stool in 7, vomiting in 6, GI bleeding, hypertension, hematemesis and palmar erythema in 3, cyanosis, Spider angioma and edema in 2 and collateral vein in 1.

The symptoms and signs were as follows at the one year after treatment were splenomegaly, jaundice, hepatomegaly, mild ascites and GI bleeding in 8,6,4 and 3 children, respectively.

Fatigue, epistaxis and hematemesis in 2, collateral vein, anorexia, fever, dark urine in 1 and abdominal pain, vomiting, hypertension, palmar erythema, cyanosis, acholic stool, Spider angioma and edema were improved.

The symptoms and signs were as follows at 2 years after treatment were splenomegaly in 3, Fatigue and epistaxis in 2, jaundice, hepatomegaly, ascites GI bleeding, hematemesis and collateral vein in one (Table 1).

Table 1: Antibodies finding in the patients with AIH

	Time			
	At First		At the one year past	
Antibody	Tested	Positive	Tested	Positive
ANA	30	4(13.33%)	10	2(20%)
AMA	29	21(72%)	9	2(2.2%)
Anti-LKM1	29	10(34%)	7	-
ASMA	29	20(68%)	9	2(2.2%)
RF	26	2(7.6%)	9	-
LE. Cell	28	-	28	-

After the diagnosis, all patients were put on prednisolone treatment (1-2 mg/kg/day, max 60 mg day^{-1}). This dose was gradually tapered by 5 mg every week after the first week of therapy and maintained on 15 mg day^{-1}. Sixteen patients received Azathioprine (1-2 mg/kg/day), all patients received Acid folic, all patients received Rocatrol, six patients received Indral and Urso, all patients received lipid solution vitamin and zinc, one patient received Sulfasalazin(she was treated for Overlap syndrome: Ulcerative colitis and AIH). Of ten patients that were in the remission after 1-2 fallows up, liver biopsy was performed again in 5 patients and was not performed in other five patients because of discontents of parents. Six of them were not in the remission, one patients died and others are waiting for liver transplantation.

DISCUSSION

AIH has associations with other autoimmune disorders (Johnson *et al*., 1993). In the present study, we did not find any evidence of associated thyroid disease, which is stated to be the most common autoimmune disease found in AIH. Alopecia and UC found in one patient. Meanwhile hemolytic anemia was not present, combs positivity was not determined in any of our patients.

Previous reports of AIH including both adults and children indicate that ANA/ASMA positive AIH (type 1 AIH) has a relatively benign course whereas LKM-1 positive AIH disease (type 2 AIH) is severe and mortality is high despite appropriate therapy (Homberg *et al*., 1987). Recently, Maggiore and Gregorio, separately concluded that the severity and long-term outcome of type 1 or type 2 AIH of childhood is similar (Gregorio and Mieli-Vergani, 1997; Maggiore *et al*., 1993). In the present study, 17 patients of them have type I of AIH and 13 patients of them have type II of AIH.

Prednisolone and Azathioprine are the major drugs of choice either used alone or in combination whether the histological appearance is that of severe hepatitis, with or without fibrosis or cirrhosis (Krawitt, 1996; Sanchez *et al*., 1992). Although patients may remain in remission or have only mild disease activity when the treatment is withdrawn, in the majority of patients therapy needs to be continued life long. There are no firm guidelines for the withdrawal of treatment (Balakrisnan *et al*., 1998). In our group, 30 patients received steroids as the initial therapy; in sixteen of them Azathioprine was added to reduce the steroid dose because of significant side effects. In all patient Acid Folic and lipid solution vitamin was used for treatment.

Balakrishnan *et al*. (1998) reported a series of 10 patients with AIH 1997. Subsequently 2 other centers from India reported their experience (Amarapurakar and Amarapurakar, 2000; Gupta *et al*., 2001).

In that study, patients with AIH formed 5.6% of all patients with liver disease. In the other Indian studies, this ratio was 3.4 and 6.4% of chronic liver disease. This is lower than the 11-23% frequency reported in North America and western European whites but similar to the 5-10% reported from Brazil (Cancado and Porta, 2001; Czaja, 2002).

There was good response to immunosuppressant, comparable to data in Western Literature (Czaja, 2002).In our study, all patients have a good response to treatment that similar to other studies.

Does AIH in our study differ from that seen in the west? Zolfino *et al*. (2002) compared European Caucasoid with other (African, Asian and Arabic) patients and found that the latter were younger, more often and feature of cholestasis on liver biochemistry and morphologic biliary changes and showed a poor initial response to standard therapy. However, our findings do not support these conclusions and 28 patients of our patients have a good response to received treatment and one patients died with encephalopathy and one patient is waiting for liver transplantation.

Autoimmune liver disease is a relatively uncommon cause of Chronic Liver Disease (CLD) in children and accounted for only 3.9% of our total cases of Chronic Liver Disease (CLD), which is similar to 2.3% reported by Gregorio *et al*. (1997). Autoimmune liver disease has been described to have a female preponderance (Gregorio *et al*., 1997; Maggiore *et al*., 1993). Twenty eight of 30 of our patients were girls. The median age of our children was 8.4 years, which is similar to that of 10 years (ranger 2-15 years) (Gregorio *et al*., 1997) and 9.7 years (reage 2-14.5 years) (Maggiore *et al*., 1993) as reported by other workers.

Autoimmune liver disease has been shown to have different forms of clinical presentation, that is, acute hepatitis-like presentation, insidious onset illness with fatigue and jaundice lasting a few months or years and the patients present either with hepatomegaly or

complications of chronic liver disease (Gregorio *et al*., 1997; Maggiore *et al*., 1993). Of these acute hepatitis-like presentation is reported to be common 25-56% (Gregorio *et al*., 1997; Czaja, 1999; Vergani and Mieli-Vergani, 2000; Maggiore *et al*., 1993). In our series, jaundice in twenty-eight patients was the most common signs of presentation of patients and spelenomegaly and hepatomegaly were other common signs of patients at presentation.

Despite the short duration of symptoms at presentation, the liver damage is usually quite advanced. Cirrhotic changes are seen in the biopsy in 63-80% of cases (Gregorio *et al*., 1997; Maggiore *et al*., 1993). Children with Autoimmune Inflammatory Liver Disease (AILD) usually respond favorably to treatment with immunosuppressive drugs, that is, biochemical activity of disease is reduced and synthetic function improve even in patients with severe impairment of liver functions (Yachha *et al*., 2001). A complete biochemical and clinical response was seen in 94% of cases on treatment with prednisiolone and AZT. Twenty eight patients of our patients have a good response and remission with immunosuppressive therapy, one patient was died and one patient will receive liver transplantation.

In 5 patients after 1-2 years treatment with prednisiolone and AZT, prednisiolone tapered. In the liver biopsy of them complete remission reported. Because, after six month treatment only with AZT, relapse in 2 of 5 patients with rise of liver enzymes observed. That prednisiolone administered again.

In the study of Oettinger *et al*. (2005), type I was the most frequent diagnosis(73%) and was more prevalent in older children.

In our patients, seventeen patients (56%) were type I and thirteen patients (44%) were type II that similar to the Oettinger R study (Oettinger *et al*., 2005).

Also, in our series, mean of age in patients with type I of AIH was higher than mean of age in patients with type II of AIH and that similar to the Oettinger R study (Oettinger *et al*., 2005) . AIH accounted for 6% of all patients with liver disease seen in the

Study of Gohar Mieli-Vergani (1997) in India. In our study, as similar as that study, AIH accounted for 5.6% of all patients with liver disease that admitted in the gastroenterology and hepatology ward of our Hospital.

CONCLUSION

In summary, AIH in childhood has a wide spectrum of clinical features that extends from the absence of symptoms to an acute, even fulminate hepatitis. Although considered rare, AIH should consider in the differential diagnosis of both acute and chronic liver diseases of children after excluding the relatively more commonly seen viral and metabolic diseases. AIH progresses to cirrhosis when left untreated, but early diagnosis and treatment prolong survival.

Type I autoimmune hepatitis was the predominant type of autoimmune hepatitis children. The majority of patients with autoimmune hepatitis presented with liver signs such as jaundice, hepatomegaly and riseing of liver function test. Autoimmune hepatitis was female predominant disease. There was good response to immunosuppressive therapy.

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