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Aydan KANSU
Ayhan Gazi KALAYCI
Buket ALTUNTAŞ
Tümay DOĞANCI
Nurten GİRGİN

Autoimmune Hepatitis in Children: A Report of Ten Cases

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Department of Paediatric, Division of Pediatric Gastroenterology, Faculty of Medicine, Ankara-Turkey

Abstract: Clinical and laboratory features and the outcome of ten cases (nine female, one male) (age range 7-14 years, mean 10.7±2.2 years) with autoimmune hepatitis are described. The diagnosis was established by the laboratory features of elevated serum transferases, hypergammaglobulinemia, presence of autoantibodies, liver histology, excluding viral and metabolic etiologies and by a prompt response to corticosteroid therapy. One patient was associated with celiac disease. Chronic active hepatitis was present histologically in seven children while in three, cirrhosis with portal hypertension had already been established. All patients received steroids. Azathioprine was instituted in three patients in addition to steroid therapy. The patients were followed up for 1-9 years (mean 4.1±3.0 years). One patient relapsed during maintenance therapy, and two patients died within less than one year probably because of poor compliance to treatment. In one patient treatment was withdrawn after three years and no relapse occurred during the six months of follow-up. Control liver biopsies were done in six patients after two years of treatment in which five showed histological improvement. We conclude that autoimmune hepatitis in childhood has a wide spectrum of clinical features including the absence of symptoms, acute hepatitis and established cirrhosis with portal hypertension. Autoimmune hepatitis should be kept in mind in the differential diagnosis of both acute and chronic liver diseases of children. Autoimmune hepatitis carries a high mortality if left untreated but has a favourable outcome when treatment is initiated early in the course of the disease.

Key Words: Autoimmune hepatitis, childhood.

Introduction

Autoimmune hepatitis (AIH) is an inflammatory liver disease of unknown etiology characterized by autoantibodies and histological features of chronic active, periportal hepatitis (1). Progressive destruction of the hepatic paranchyma often progresses to cirrhosis and it carries a high mortality if untreated (2). AIH has two peaks of incidence, one being between the ages of 10 and 20 (1). Only a few large series of children with AIH have been reported (2-6). We present clinical and laboratory features and the outcome of ten children with AIH.

Materials and Methods

Ten patients diagnosed as having AIH in our center are presented. Of the ten children, nine were girls and one was a boy, mean age 10.7±2.2 years (range 7-14 years). Diagnosis was based on routine biochemical and immunologic analysis, histopathology of the liver and exclusion of viral and metabolic etiologies. Drug consumption or exposure to toxic agents were excluded in all patients. Hepatitis B virus, hepatitis C virus, Epstein-Barr virus and Cytomegalovirus were excluded by appropriate serologic markers. Wilson's disease was excluded in all by normal serum ceruloplasmin and normal 24-hour 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 (SMA) and liver-kidney-microsomal antibody (LKM-1) were tested at a dilution of 1:10 in phosphate-buffered saline by indirect

immunofluorescence. Serum immunoglobulin concentrations were measured by laser nephelometry (Behringwerke AG, Marburg, Germany).

Liver histology was interpreted using conventional criteria (7).

Treatment: After the diagnosis, all patients were put on prednisolone treatment at a dose of 2 mg/kg/day (maximum 60 mg/day). 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 (2 mg/kg/day) was added to steroid therapy in three 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 three patients Azathioprine was used temporarily due to the development of cataract. No other immunosuppressants were used.

Results

The symptoms were as follows: jaundice in nine (six of them acute onset, and three relapsing), epistaxis in two and anorexia, fatigue and malaise in four. One patient had no symptoms attributable to liver disease, she was admitted to hospital for evaluation of short stature and chronic diarrhea, and celiac disease was diagnosed based on serology and histological criteria. AIH was diagnosed in this patient with further evaluation when persisting enzyme elevation was noticed.

In three out of the ten children, the duration of symptoms was more than six months while in six, it was between a week to four months (mean 23.1±22.6 week). One patient had no symptoms attributable to liver disease. Pathological physical examination findings at presentation were icterus in eight, hepatomegaly in nine, splenomegaly in six and ascites in one. Physical findings of chronic liver disease such as spider nevus and palmar erythema were found in two patients. In one patient (case 2), the only pathologic finding at examination was short stature.

Portal system Doppler ultrasound and/or upper gastrointestinal endoscopy was performed for evaluation of the presence of portal hypertension which revealed positive results in six patients.

Demographical characteristics, symptoms and physical examination findings of the patients are shown in Table I.

All of the children had a 4 to 15 fold elevation of ALT. IgG levels were above 20 g/L in all patients, in seven of them it was above 30 g/L. All but one were ANA and/or SMA positive (titer range, 1/40-1/160). In eight of these patients, ANA and/or SMA positivity was found at presentation while one became ANA positive after two months of steroid treatment. In the patient without ANA and/or SMA positivity, the diagnosis was confirmed by laboratory features of elevated serum transferases, hypergammaglobulinemia, liver histology and by rapid response to corticosteroid therapy. We were able to analyse LKM-1 antibody only in four recently diagnosed patients in whom the results were negative. Coombs tests were positive in two, but neither of them had hemolytic anemia. None had anti-thyroid, anti-insulin or anti-islet cell antibodies. One patient had an associated disorder, celiac disease (case 2). Liver histology revealed chronic active hepatitis with portal tract inflammation, periportal/periseptal necrosis and lymphocytic aggregate in three patients. In four patients septal bridging fibrosis was found in addition to the above histologic findings, while in three, definite cirrhosis was present. Table II shows the laboratory and liver histologic features of the patients.

After the diagnosis, all patients were put on prednisolone treatment (2 mg/kg/day, max 60 mg/day). This dose was gradually tapered by 5 mg every week after the first week of therapy and maintained on 15 mg/day. Three patients received Azathioprine (2 mg/kg/day) in addition to steroid therapy because of significant side effects (glucose intolerance in two patients during the second and third months of therapy and hypertension in one patient during the first week of therapy). In three patients, cataracts developed during the second year of therapy which regressed in two months after switching to Azathioprine and did not recur after re-administration of steroids. Psychiatric symptoms such as delirium, depression or attempted suicide were observed in three of the children during the initial phase of treatment. In one patient intraocular pressure was elevated temporarily. The longest duration of treatment in our group is nine years. Therapy was withdrawn in one patient after 3 years due to histologic resolution. At the time of writing she had been off therapy for 6 months without recurrence. During the period of observation (1-9 years, mean: 4.1±3.0 years), one patient had an episode of relapse during maintenance therapy which responded to an increased dose of prednisolone. One patient was lost to follow-up after one year, and one patient was followed up in another hospital. Among the ten patients, except for one lost to follow-up, seven of them are alive, six on maintenance therapy and one off therapy (at the time of writing). Two patients died within less than one year (8 and 10 months) after the diagnosis

Table 1. Demographical characteristics, symptoms and physical examination findings of the patients.

No	Name, Sex, Age (years)	Symptoms	Duration of symptoms	Physical examination findings	Portal hypertesion
1	(M.Ö), F, 11	jaundice, vomiting	1 week	icterus, hepatosplenomegaly	-
2	(B.E), F, 13	no symptoms		H_{SDS}: -3,05 W_{SDS}: -2.40	-
3	(F.G), F, 14	jaundice, malaise, fatigue, anorexia	2 weeks	icterus, hepatomegaly	-
4	(F.G), F, 12	jaundice, epistaxis	16 weeks	icterus, hepatomegaly	+
5	(F.K), F, 8	jaundice, malaise, fatigue, anorexia	1 week	icterus, hepatosplenomegaly	-
6	(H.A), F, 9	jaundice, malaise, fatigue	16 weeks	icterus, hepatosplenomegaly, ascites	+
7	(E.A), F, 7	epistaxis, relapsing jaundice	52 weeks	icterus, hepatosplenomegaly	+
8	(B.E), M, 12	relapsing jaundice	52 weeks	hepatomegaly, spider nevus, palmar erythema, gynecomastia	+
9	(S.H), F, 11	jaundice, malaise, fatigue	16 weeks	icterus, hepatosplenomegaly, spider nevus	+
10	(H.O), F, 10	relapsing jaundice	52 weeks	icterus, hepatosplenomegaly	+

probably due to poor compliance to treatment. Control liver biopsies were performed in six patients after two years of treatment in which five showed histological improvement. In four of these patients, significant histological improvement was demonstrated (minimal to mild disease activity), while in one, chronic active hepatitis with bridging necrosis persisted which had cirrhosis initially. The patient who relapsed showed no histological improvement. Treatment, complications, and follow-up results of the patients are shown in Table III.

Discussion

Autoimmune hepatitis (AIH) is a rather uncommon progressive inflammatory liver disease characterized histologically by dense mononuclear cell infiltrates in the portal tracts and serologically by the presence of nonorgan and liver specific autoantibodies in the absence of a known etiology (1). The etiology and the pathogenesis of AIH remain largely unknown but the loss of tolerance against autologous liver tissue in a genetically predisposed host exposed to an environmental agent is regarded as the principal pathogenetic mechanism (8, 9). Environmental triggering agents are unknown but some viruses or drugs such as measles, hepatitis C, Ebstein Barr, hepatitis A virus or interferon treatment are thought to trigger AIH (8, 10). Untreated AIH carries an unfavorable prognosis and many cases progress to cirrhosis with high mortality, therefore the diagnosis should be made as soon as possible (2). With treatment however, the survival rate improves (11).

Earlier descriptions of the disease noted its chronic, but fluctuating course and it was generally accepted that for a diagnosis to be made, six months' duration of symptoms were required. Patients most often present with insidious onset of malaise, anorexia and fatigue but other presentations include advanced cirrhosis with findings of portal hypertension, apparent acute hepatitis with jaundice resembling viral hepatitis and a severe fulminant course (12-14). Completely asymptomatic cases in which the disease is discovered when abnormal serum enzyme values are obtained at routine health screening have also been described (15). Reports suggest that a 6-month duration of hepatic illness should not be a prerequisite for the diagnosis of AIH (16, 17). In our group of AIH patients, only three out of the ten children had a history of hepatic symptoms of six or more months of duration while in six of them the duration of symptoms was between a week and four months. One patient had no symptoms at all attributable to liver disease. Three of the patients presented like an acute viral hepatitis, while in three, advanced cirrhosis with portal hypertension had already been established at the time of diagnosis.

Conventional diagnostic criteria include three to ten fold elevations of serum aminotransferase activities, hypergammaglobulinemia, high titers of circulating ANA, SMA or LKM-1 and exclusion of all other possible etiological factors (1, 8, 9). It is agreed that for children, lower titers of antibodies are sufficient for a diagnosis of

Table 2. Laboratory and liver histologic features of the patients.

Patient no	ALT (U/L)	IgG (g/L)	ANA	SMA	LKM	Coombs	Anti-thyroid antibody	Anti-insulin antibody	Anti-islet cell antibody	Histologic features
1	328	48.7	+	+	-	+	-	-	-	CAH** (bridging necrosis)
2	171	24.6	+	+	-	+	-	-	-	CAH
3	430	30.7	-	+	-	-	-	-	-	CAH (bridging necrosis)
4	126	25.4	+	-	ND*	-	-	-	-	CAH (bridging necrosis)
5	481	41.8	-	+	-	-	-	-	-	CAH (bridging necrosis)
6	230	42.2	+	-	ND	-	-	-	-	CAH
7	239	51.0	+	+	ND	-	-	-	-	CAH
8	139	47.2	+	+	ND	-	-	-	-	Cirrhosis
9	112	45.5	-	-	ND	-	-	-	-	Cirrhosis
10	234	25.3	+	-	ND	-	-	-	-	Cirrhosis

* ND: Not done

** CAH: Chronic active hepatitis

Table 3. Treatment, complications and follow-up results of the patients.

Patient no	Treatment	Duration of treatment	Complications of treatment	Duration of follow-up	Control biopsy	Status
1	steroid	2 years (still continuing)	cataract	2 year	mild disease activity	Alive
2	steroid	5 years (still continuing)	-	5 years	mild disease activity	Alive
3	steroid	3 years (steroid therapy withdrawn)	cataract	3.5 years	minimal disease activity	Alive
4	steroid+ AZA*	9 years depression, delirium	glucose intolerance, 9 years	CAH** (bridging necrosis)	Alive	
5	steroid	3.5 years (still continuing)	cataract	3.5 years	mild disease activity	Alive
6	steroid	2 years	depression, attempted suicide	lost to follow-up	ND***	?
7	steroid	1 year	glaucoma	follow-up in another hospital	ND	Alive
8	steroid	8 years	-	8 years	CAH (bridging necrosis)	Alive
9	steroid+ AZA*	10 months	hypertension, delirium	1 year	ND	Exitus
10	steroid+ AZA*	8 months	glucose intolerance	1 year	ND	Exitus

* AZA: Azathioprine

** CAH: Chronic active hepatitis

*** ND: Not done

AIH (1). In childhood, AIH is associated with either the presence of ANA/SMA antibody in the serum which is classified as type 1 AIH or with the LKM-1 antibody in the serum which is called type 2 AIH (18). In the present study, all had 4 to 15 fold elevated levels of ALT, all but one had ANA/SMA positivity in a titer of 1/40 or more. Gregorio et al. (2), in their large series of 52 children, reported ANA/SMA positivity in 32 children. We were not

able to analyse other antibodies described to be present in AIH such as antiactin, anti liver pancreas, soluble liver or liver cytosolic antibodies (19), yet LKM-1was negative in four children in whom the test could be done. The diagnosis in the patient without detectable antibodies was established by the laboratory features of elevated serum transferases, hypergammaglobulinemia, liver histology, excluding viral and metabolic etiologies and by a prompt response to corticosteroid therapy.

AIH has associations with other autoimmune disorders (1). 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. Although hemolytic anemia was not present, Coombs positivity was determined in two of our patients which became negative soon after initiation of steroid therapy. One interesting finding in our group was a case associated with celiac disease. Reversible liver involvement of a wide spectrum ranging from asymptomatic transaminase elevations to chronic active hepatitis or cirrhosis is well known in active phase of celiac disease (20, 21). On the other hand, an increased prevalence of autoimmune diseases among celiac subjects and an increased prevalence of celiac disease among those affected by autoimmune diseases have long been known (22). This prevalence is ascribed to shared genetically predisposing factors, especially some HLA antigens. Primary biliary cirrhosis and primary sclerosing cholangitis have been reported to be associated with celiac disease (23, 24). In the literature, there are only a few cases describing the association between celiac disease and AIH (25-27). The case of AIH associated with celiac disease presented in this series, had classical symptomatology, physical findings, laboratory features, and histological findings of gluten sensitive enteropathy. She had been followed up for six months with gluten-free diet, but her ALT elevation persisted. Liver enzyme elevations seen in some celiac patients are reported to be normalized after gluten-free diet within one to three months (20). It was her persisting aminotransferase elevations which necessiated a work-up for chronic liver diseases during which she was diagnosed as having AIH with hypergammaglobulinemia, presence of ANA and SMA antibody, and histological findings in a liver biopsy. We think that the association of celiac disease in our relatively small group of AIH deserves attention.

Previous reports of AIH including both adults and children indicate that ANA/SMA 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 (28). Recently, Maggiore and Gregorio, separately concluded that the severity and long-term outcome of type 1 or type 2 AIH of childhood is similar (2, 3). In the present study there was only one patient who was negative for ANA and SMA and the LKM status is unknown. So it is impossible to comment on the outcome of the different two subtypes of AIH in our study group.

Prednisolone and Azathioprine are the major drugs of choice either used alone or in combination whether the histological appearence is that of severe hepatitis, with or without fibrosis or cirrhosis (8, 29). 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 (8). In our group all the patients received steroids as the initial therapy; in three of them Azathioprine was added to reduce the steroid dose because of significant side effects. In two other patients Azathioprine was used only temporarily because steroids had to be stopped due to cataract formation. We attempted to withdraw the drug only in one patient and she continued to be in remission for 6 months at the time of writing. Seven out of the ten children in the present study were alive for the observation period of 4.1±3.0 years. The two patients who died a few months after diagnosis, and the one who relapsed, were the children who received Azathioprine in combination with steroids and they were actually the patients with poor treatment compliance. It is impossible to compare the efficacy of steroids with Azathioprine therapy in our relatively small group of children with AIH but we can conclude that AIH in childhood has a favorable outcome when treatment is initiated early in the course of the disease.

It has been stated that treatment failures occur in about 20% of patients with AIH and that it is more frequent in those with established cirrhosis and in general, the prognosis is inversely correlated with the histological severity of the disease. Indeed, the two patients in our series who died were the patients presented initially with histologically proven cirrhosis associated with portal hypertension. The clinical history of one of them included relapsing jaundice for a year before therapy was instituted. These observations confirm the opinion of needing to diagnose and to institute the treatment as soon as possible (8). Based on our observations, we also conclude that fibrosis of the liver may be resolved in AIH following protracted and effective treatment. In all of our patients with good compliance to treatment, significant histologic improvement was demonstrated within two years of therapy.

In summary, AIH in childhood has a wide spectrum of clinical features that extends from the absence of symptoms to an acute, even fulminant hepatitis. Although considered rare, AIH should be kept in mind 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.

Correspondence author:
Ayhan KANSU
Yılmaz Çolpan Sok. 46/1
OR-AN Sitesi 06450 Ankara-TURKEY

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