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OUTCOME OF AUTOIMMUNE HEPATITIS IN CHILDREN

Long-term outcome of autoimmune hepatitis in children

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Abstract

Background and Aim: Autoimmune hepatitis (AIH) is a chronic disease of unknown etiology, which usually progresses to cirrhosis if not diagnosed and treated promptly. Data on long-term follow up in children with AIH are scant. The aim of this study is to assess the long-term outcome of autoimmune hepatitis in children with respect to clinical and laboratory features at presentation.

Methods: Data were extracted from the medical records of patients presenting over a 28-year period (1972–2000) to the Royal Children's Hospital, Melbourne, Australia. Additional information was obtained by interviewing patients, and their current physicians. Of the 30 patients (22 females, mean age 9 years) identified, 18 had type I, three had type II, four had autoimmune–polyendocrinopathy syndrome type 1, one had infantile giant-cell hepatitis associated with Coomb's-positive hemolytic anemia, and four were seronegative (antinuclear antibody (ANA), smooth muscle antibody (SMA) and liver–kidney microsomal antibody (LKM)).

Results: Clinical features at presentation included hepatomegaly (86%), jaundice (66%) and splenomegaly (50%). Initial investigations revealed a median serum bilirubin level of 55 μmol/L (range 6–425), median aspartate aminotransferase level of 678 IU (range 70–2548), and abnormal clotting in 33% of patients. Liver biopsies were performed on all patients at presentation and 11 showed cirrhosis (36%). The mean follow-up period was 10.0 ± 7.8 years with 43% being followed for > 10 years. Only two patients died and one required transplantation. Fourteen (50%) patients continue to be on low dose prednisolone with azathioprine, two (7%) are on prednisolone alone, and six (21%) are on no therapy. When the cirrhotic and non-cirrhotic patients were compared, the albumin level at presentation was significantly lower in the cirrhotic group ($P = 0.01$). Of the patients who were cirrhotic at presentation, six (54%) remain compensated with a mean follow-up period of 8 years. All 24 patients currently under follow up are engaged in age-appropriate activities including school, part- or full-time work.

Conclusion: Autoimmune hepatitis has a favorable long-term outcome with a transplant-free survival rate of 90% over a mean period of 10.0 ± 7.8 years (range: 0.5–23), and a normal or near-normal lifestyle irrespective of presenting clinical, laboratory or histological features.

Key words: autoimmune hepatitis, children, liver–kidney microsomal antibodies, polyendocrinopathy syndrome, smooth muscle antibodies.

INTRODUCTION

Autoimmune hepatitis is a disorder of unknown etiology characterized histologically by dense mononuclear cell infiltrates in the portal tracts, progressive destruction of the hepatic parenchyma, and serologically by the presence of circulating non-organ and liver-specific autoantibodies.[1]

Steroids, with or without azathioprine, have convincingly altered the outcome in most patients.[2–6] Without treatment, autoimmune hepatitis (AIH) often progresses to cirrhosis, and in the more severe cases, carries

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a high incidence of mortality and a low rate of spontaneous remission.[7]

Reported series of autoimmune hepatitis in children in the literature are scant.[8–12] Two main forms have been described in children: type I associated with antinuclear and/or antismooth muscle (ANA/SMA) antibodies, and type II is associated with antiliver-kidney microsomal antibodies type 1 (LKM-1). The proposed target for antismooth muscle antibodies in AIH is the actin microfilament, while antismooth muscle antibodies directed to non-actin microfilaments can be found in other conditions, like viral hepatitis. The anti-liver–kidney microsomal antibody type 1 is usually directed against cytochrome P450IID6.[13]

Although these two types of AIH have different clinical, biochemical and histological features, they have been reported to have similar severity and outcome.[11]

In the two largest series of children with AIH published,[11,12] one reported a median follow up of 5 years while the other reported a mean follow up of 4 years and 10 months. Only one of the studies[11] attempted to identify factors predictive of long-term outcome.

In this study, we describe 28 years of experience with AIH, with special emphasis on long-term outcome (mean follow up of 10 years).

METHODS

Patients with AIH presenting to the Gastroenterology and Hepatology service at the Royal Children's Hospital, Melbourne between 1972 and 2000 were included in the present study. Data were collected by reviewing the medical records, phone follow up with the patients themselves and their families, as well as the medical care provider for those who graduated from pediatric care.

All patients were seronegative for hepatitis B surface antigen. Hepatitis C infection was excluded in all patients who presented after the availability of the hepatitis C virus ELISA assay (15 patients), and retrospectively during follow up for the graduates, with the exception of three patients who were lost to follow up and two patients who died before being tested. Other possible causes of hepatitis were excluded by using appropriate investigations.

At diagnosis, patients were treated with prednisolone starting at 2 mg/kg per day (maximum of 60 mg/day), followed by a gradual tapering according to the clinical response and transaminase activity. Azathioprine (1–2 mg/kg per day) was added to prednisolone, if an increase in the aspartate aminotransferase (AST) level was noticed during the tapering of the prednisolone dose. Patients were followed up regularly with close monitoring of the disease activity both clinically and by liver function tests, aiming to achieve control with minimal immunosuppressive therapy. Treatment was discontinued if the patient maintained remission for a minimum of 2 years, as defined by the absence of clinical symptoms, normal transaminases, and absence of necroinflammatory activity on a liver biopsy. Patients unresponsive to the immunosuppressive therapy, with deterioration in liver function, were listed for liver transplantation when this became available in 1988.

The follow-up data collected included: presence of jaundice, splenomegaly, current immunosuppression, complications of treatment, survival, liver transplantation, and age-appropriate activity, including work and education.

Statistical analysis was performed by using Stata Statistical software: Release 6.0. (Stata Corporation, College Station, TX, USA). Fisher's exact test was used for categorical variables, and Wilcoxon's rank-sum (Mann–Whitney) test was used for continuous variables. Results are expressed as either median or mean value ± SD. A P value < 0.05 was considered to be significant.

RESULTS

Thirty patients with AIH were identified during the study period. Eighteen patients had type I with ANA and/or SMA antibodies, three patients had type II with LKM-1 antibodies, and four patients had AIH, which was negative for ANA/SMA and LKM-1 antibodies. When classified according to the International Autoimmune Hepatitis Group scoring system,[1] 15 patients had definite and the other 10 had probable AIH. In addition, four patients had autoimmune polyendocrinopathy syndrome type 1 (APS-1), and one patient had infantile giant cell hepatitis with associated autoimmune Coomb's-positive hemolytic anemia.

Clinical data

The clinical features at presentation are summarized in Table 1. Twenty-two patients were female (73%), with a mean age at presentation of 9.4 ± 4.2 years (range 1–15).

A family history of extrahepatic autoimmune disease in the first-degree relatives was positive in seven patients; systemic lupus (two), rheumatoid arthritis (two), autoimmune thyroiditis (one) and in siblings (brother and sister) with APS-1.

The onset of the disease followed three patterns: (i) acute onset of hepatitis was observed in nine patients, progressing to fulminant hepatic failure in one. There was a history of previous episodes of hepatitis-like illness in three of the patients (2, 3 and 6 years prior to diagnosis); (ii) insidious onset of anorexia, fatigue and mild intermittent jaundice was observed in 13 patients, with two of these found to have evidence of disturbed synthetic function of the liver and ascites at the time of presentation; and (iii) an incidental finding of abnormal liver function tests or hepatosplenomegaly during follow up for another medical problem was seen in eight patients.

Included in this series are four patients with APS-1, with clinical characteristics being shown in Table 2. Also included is one patient with autoimmune Coomb's-positive hemolytic anemia, who presented at 9 months of age with anemia, and was treated with prednisolone. At 11 months of age, he developed jaundice, had elevated liver enzymes and deteriorating liver function. A liver biopsy showed severe hepatitis with giant cell transformation. He was treated unsuccessfully with

Table 1 Clinical features at presentation in 30 patients with autoimmune hepatitis

	Frequency	Percentage (%)
Hepatomegaly	26	86
Tiredness	22	73
Jaundice	20	66
Spider angiomata	20	66
Splenomegaly	15	50
Anorexia	10	33
Vomiting	10	33
Abdominal pain	10	33
Dark urine	9	30
Pale stool	6	20
Epistaxis	4	13
Hematemesis	3	10
Bruising	3	10
Ascites	3	10
Edema	2	6
Palmar erythema	2	6
Digital clubbing	1	3
Associated autoimmune disorders		
APS-1	4	13
Insulin-dependent diabetes	3	10
Systemic lupus	2	6
Ulcerative colitis	2	6
Thyroiditis	2	6
Autoimmune hemolytic anemia	1	3
Pemphigus vulgaris	1	3
Mikulicz's syndrome	1	3

APS-1, Autoimmune polyendocrinopathy syndrome type 1.

prednisolone, azathioprine, cyclosporine and intravenous immunoglobulin. Repeated liver biopsy prior to immunoglobulin treatment showed progression to cirrhosis. The patient started to improve very slowly over the subsequent 5 years. He is currently 7-years-old, on 2 mg prednisolone and 25 mg azathioprine with normal growth, normal liver function tests and hemoglobin, but has bilateral cataracts.

All three patients with insulin-dependent diabetes mellitus had this diagnosis made between 2 and 4 years prior to the diagnosis of autoimmune hepatitis. One of these was not treated with steroids as she had very poorly controlled diabetes. The other two patients received full dose prednisolone without any significant impact on diabetic management.

Laboratory data

The median level for serum bilirubin at presentation was 55 μmol/L (range 6–425, normal value (nv): < 20). Eleven patients had a raised globulin level of more than 1.5-fold the upper limit of normal (ULN), mean 46.0 ± 17.6, range 24–84, nv: 24–33 g/L. Immunoglobulin levels were performed in 16 patients. Immunoglobulin (Ig)G and IgM isotypes were high in nine and eleven patients respectively, and two had low IgA with some patients having more than one abnormality. The mean value for serum albumin was 37.0 ± 11.6 g/L (range 17–74, nv: 35–50). In 23 patients (76.6%), AST exceeded fivefold the ULN, with a median of 678 IU/L (range 70–2548, nv: < 50). Abnormal clotting at presentation was observed in 10 patients (33%). Antinuclear antibodies (ANA) were found to be positive in

Table 2 Clinical, biochemical, and histological characteristics of patients with autoimmune polyendocrinopathy syndrome type-1

Patient	Sex	Age at presentation	Associated problems	AST (×ULN)	Antibodies	Histology
1	F	9 years	Hypoparathyroidism Mucocutaneous candidiasis	33	Anti-thyroglobulin	Chronic active hepatitis
2	F	10 years	Hypoparathyroidism Mucocutaneous candidiasis Hypoaldosteronism Addison	3	Anti-LKM Anti-acetylcholine receptor Anti-adrenal	Chronic active hepatitis
3	M	15 years	Hypoparathyroidism Mucocutaneous candidiasis Addison Alopecia Steatorrhea Growth failure	1.5	None	Subacute hepatitis
4	F	3 years	Hypoparathyroidism Mucocutaneous candidiasis Pernicious anemia Growth failure Primary ovarian failure	17	ANA Anti-mitochondrial	Chronic active hepatitis

AST, aspartate aminotransferase; Anti-LKM, anti-liver–kidney microsomal antibodies type 1; ANA, antinuclear antibodies; ULN, upper limit of normal.

16 patients. The pattern of immunofluorescence was reported in 12 of these patients; homogeneous in four, speckled in four, and mixed in four.

Histological data

All patients underwent a liver biopsy, obtained by the percutaneous route prior to starting treatment, except for one patient in whom the procedure was delayed until after the commencement of steroid therapy because of severe blood clotting disturbance. The main histological features at presentation were: portal tract inflammation (29), portal tract fibrosis (20), piecemeal necrosis (19), bridging necrosis (11), lobular inflammation (eight), and cirrhosis (11). Twenty follow-up liver biopsies were done in 15 patients. The first follow-up biopsy was done at a mean of 2.0 ± 1.5 years from the initial biopsy. Twelve patients demonstrated an improvement of necroinflammatory changes, one had no improvement, and two progressed to cirrhosis in spite of immunosuppressive therapy.

Characteristics of patients presenting with cirrhosis are shown in Table 3. None of the four patients with APS-1 or the patient with autoimmune (AI) hemolytic anemia had cirrhosis at the time of presentation.

Treatment

Twenty-nine patients were initially treated with prednisolone with a starting dose of 2 mg/kg followed by gradual weaning once liver function tests showed sustained improvement. The lowest dose of steroid found to maintain remission was 5.2 ± 1.6 mg, which was achieved in a median time of 10 months (range 1–153 months) from the start of steroid treatment. The initial response to prednisolone as defined by a drop of AST to less than twice the ULN within the first 3 months was observed in 25 patients (83%). Nineteen patients were Cushingoid in the early stages of prednisolone treatment, but improved with reduction of the dose. Other side-effects were: osteoporosis (six), serious infection (four), hypertension (four), acne (three), epigastric pain (three), behavioral disturbance (three), growth disturbance (two), proximal muscle weakness (one), and cataract (one). Azathioprine was required in 14 patients after a median time of 3 months (range 0.23–24) following steroid treatment. None of the patients had developed signs of significant bone marrow suppression because of treatment with azathioprine.

Outcome

Thirty patients with AIH were followed for a mean of 10.0 ± 7.8 years (range, 0.5–23). Twenty patients (66%) were followed up for ≥ 5 years, 13 (43%) for ≥ 10 years, and five (16.6%) for ≥ 20 years.

Two patients died because of liver failure before liver transplantation became available. One of these patients had type I AIH while the other was seronegative. One patient (type I AIH) was transplanted 8 years after diagnosis because of portal hypertension, recurrent peritonitis and hepatorenal syndrome. He is alive and well 5.5 years after the transplant without evidence of recurrence in the graft.

Fourteen relapses (all while weaning prednisolone) were recorded in 10 patients under our care, with median follow up of 8 years. The mean time to the first relapse was 3.9 ± 2.8 years after the initiation of steroid treatment. Three patients had a subsequent relapse at a mean of 2.70 ± 0.23 years from the first relapse. All cases responded to bolus treatment with prednisolone. Among the survivors (Fig. 1), six patients ceased treatment without relapse, and 18 are still on treatment

Table 3 Characteristics of patients presenting with and without cirrhosis

	Patients with cirrhosis ($n=11$)	Patients without cirrhosis ($n=19$)	P value
Age (years)*	11.4 ± 3.3	8.3 ± 4.3	0.05
Sex (M/F)	5/6	5/14	0.25
Serum bilirubin (μmol/L)*	78.8 ± 65.6	94.5 ± 118.0	0.73
Serum albumin (g/L)*	30 ± 7	40.0 ± 12.3	0.01†
AST (IU/L)*	865.7 ± 617.0	946 ± 856	0.75
Abnormal clotting	4	6	1.0
Current treatment			
None	1	5	0.6
Steroid	1	3	
Steroid & azathioprine	5	9	
Outcome			
Follow up (years)*	7.0 ± 4.8	12.0 ± 8.7	0.19
Splenomegaly	0/8	5/17	0.14
Deaths	2	0	0.09
Transplant	1	0	

AST, aspartate aminotransferase. *Values are expressed as mean ± SD. †Significant.

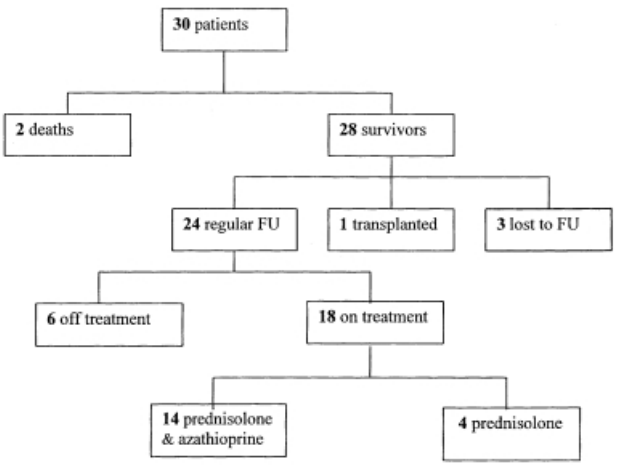

Figure 1 Follow-up (FU) data on 30 patients with autoimmune hepatitis.

(prednisolone alone in four and a combination of low-dose prednisolone and azathioprine in 14). Three were lost to follow up after a period of 1.3, 4 and 15 years care, respectively. Among the 24 patients followed up, five patients had splenomegaly within a mean follow up of 19.0 ± 4.5 years. One of these patients is jaundiced because of a recent flare up of his disease and is on both prednisolone and azathioprine. Only one of these patients had GI bleeding and required variceal banding.

Three female patients have had children. All surviving patients are engaged in age-appropriate activity including school, part- or full-time work. Thirteen patients are still attending our clinic regularly.

DISCUSSION

This is one of only three large series of autoimmune hepatitis in children, and has the longest follow-up period with a mean of 10 years. Type II AIH constituted only 13% of the study population in contrast to the series by Gregorio *et al.*[11] in which 38% were type II AIH. This may be because of the different genetic backgrounds in Europe from where the other series originate. Although immunofluorescence for LKM is a difficult test to perform, we do not feel that failure to detect it is the cause for our low number of type II. High titers of SMA identified in most type I patients suggest that these are likely to reflect true type I disease. In addition, there were only four patients in whom typical autoantibodies could not be identified. These so-called seronegative patients have been described,[14] and may be positive for one of the other markers including hepatocyte-specific asialoglycoprotein receptor (ASGP-R), soluble liver antigen (SLA) and liver-cytosolic antigen, which were not tested for.

We also included in this series four patients with APS-1, which is known to be associated with autoimmune hepatitis, and considered as an important determinant of fatality.[15] The autosomal locus has been assigned to chromosome 21q22.3 by linkage analysis in 14 Finnish families.[16] Cytochrome P450 1A2 has been regarded as the hepatic autoantigen in APS-1,[17] and antibodies against this antigen have important diagnostic implications. Of particular interest in our series is that all four patients were easily controlled with prednisolone alone, and indeed this was ceased in one patient. Autoimmune hepatitis appeared to play a minimal role in the morbidity associated with this condition.

One patient had severe giant cell hepatitis with Coomb's-positive autoimmune hemolytic anemia, and this entity has been regarded as a form of AIH that carries high fatality if not recognized and treated promptly.[18–20] This patient, currently 7 years old, has survived the initial fulminant course of his illness, adding to the three published cases who have survived to date.

The optimum duration of AIH treatment with immunosuppression is not very clear, and the recurrence rate after discontinuation of immunosuppression is high in both adults[21,22] and children.[9,10] We have been unable to wean the majority of our patients off steroids; however, we are able to maintain them on low-dose steroids in addition to azathioprine, which is compatible with a fairly normal life. It is important to note that attempts to wean resulted in relapses (14 in 10 patients), suggesting that long-term steroid usage is required in these patients.

All patients in this series had a liver biopsy at presentation, and hence the presence of cirrhosis could be accurately determined. Patients presenting with cirrhosis had a significantly lower albumin at presentation ($P = 0.01$) and tended to have a poorer outcome in terms of mortality and the need for transplantation ($P = 0.09$).

The overall outcome of patients in this series, however, was very favorable with only two deaths and one patient requiring a transplantation; however, none of these events occurred in the group with APS-1, or in the child with hemolytic anemia. When considering only the 25 patients with definite or probable AIH (types I, II and seronegative), the mortality in this series of two (8%) is similar to the six (11%) reported by Gregorio *et al.*,[11] and two (6%) reported by Maggiore *et al.*[12] This occurred despite the relatively high percentage of patients with cirrhosis at presentation (44% in this series, 59% of the cases by Gregorio *et al.* and 80% of the cases by Maggiore *et al.*), and suggests that these patients may remain stable for many years. The majority of our patients are engaged in age-appropriate activities including school, part- or full-time work, suggesting that morbidity from this disease does not preclude a normal lifestyle.

In conclusion, our experience with childhood AIH would suggest that the majority of patients require long-term therapy, however, survival with a reasonable quality of life is the norm.

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