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[CLINICAL TRANSPLANTATION: ARTICLES]

ORTHOTOPIC LIVER TRANSPLANTATION FOR AUTOIMMUNE HEPATITIS AND CRYPTOGENIC CHRONIC HEPATITIS IN CHILDREN[1]

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▼ Abstract

Background. Autoimmune hepatitis (AIH) and cryptogenic chronic hepatitis (CCH) are important causes of liver failure in children, frequently necessitating orthotopic liver transplantation (OLT). The aim of this study is to review disease progression and potential differences between subgroups of children with AIH and CCH.

Methods. The medical records of 65 children diagnosed with AIH or CCH between 1980 and 1998 were evaluated.

Results. The median age at presentation was 9 years, 8 months (range 4 months–19 years), and the median follow-up period was 8 years (range 3 months–18 years, 10 months). Forty-one patients (63%) were female. Twenty-eight patients were Hispanic, 28 were Caucasian, 8 were African-American, and 1 was Asian. Forty-three

patients (66%) were diagnosed with type 1 AIH, 8 (12%) with type 2 AIH, and 14 (22%) with CCH. Forty patients (62%) underwent OLT (51% of those with type 1 AIH, 75% of those with type 2 AIH, and 86% of those with CCH). Thirteen (33%) of the transplanted patients experienced disease recurrence. African-American patients experienced a significantly higher rate of disease recurrence post-OLT than did Hispanic patients. Seven patients (11%) died, two without OLT, and five posttransplantation.

Conclusions. AIH and CCH frequently necessitate OLT in children. CCH is a more aggressive disease than Type 1 AIH among children with these disorders. Ethnicity influences the rate of disease recurrence after liver transplantation.

INTRODUCTION

Autoimmune hepatitis (AIH) is a disorder described histologically by periportal inflammation, interface hepatitis, and plasma cell infiltrate in the liver and serologically by the existence of organ or nonorgan specific autoantibodies (1,2). At least two subclassifications of AIH have been proposed based on distinctive immunoserological markers, and corresponding numerical designations are often given. However, the validity and utility of these subclassifications are still uncertain (3,4).

Type 1 AIH, the most common form of the disease, is associated with the presence of antinuclear antibodies (ANA) or smooth muscle antibodies (SMA), hypergammaglobuinemia, and human leukocyte antigen (HLA) types A1, B8, DR3, and DR4 (5–7). It is typically found in adult females and tends to respond well to corticosteroid therapy (5). Type 2 AIH is associated with the presence of liver-kidney microsome type 1 (LKM-1) antibodies directed against cytochrome P4502D6, and most frequently occurs in younger children. Reports in both children and adults suggest a relatively poor response to corticosteroid therapy. Patients with type 2 AIH often undergo orthotopic liver transplantation (OLT) (8–11).

Cryptogenic chronic hepatitis (CCH) is an adjunct form of autoimmune-associated liver disease, characterized histologically by the presence of periportal fibrosis and dense mononuclear cell infiltrate and serologically by the absence of classic markers. Other autoantibodies, such as those to perinuclear-staining antineutrophil cytoplasm, the hepatic asialoglycoprotein receptor, liver-specific cytosolic antigen, liver-pancreas antigen, and glycosphingolipid in hepatocyte plasma membrane, may, instead, be present (12). The diagnosis may only be made after other causes of chronic liver disease (including metabolic, viral, and toxic) have been ruled out. CCH has a variable response to conventional therapy and is associated with other features suggestive of AIH, such as hypergammaglobulinemia, elevated total serum protein with decreased serum albumin, and HLA types B8 and DR3 (13).

The goals of this study are to evaluate disease progression, need for OLT, recurrence posttransplantation, and outcome in a multicenter series of children with AIH or CCH. We also explore potential differences among patient subgroups.

PATIENTS AND METHODS
Subjects

Patient charts were reviewed from the following referral centers: University of California-Los Angeles (UCLA) Medical Center, University of California-San Francisco Medical Center, and Southern California Permanente Medical Group. Inclusion and exclusion criteria for the diagnosis of type 1 and type 2 AIH were established using current guidelines of the International Autoimmune Hepatitis Group (12). Patients were excluded if they harbored infectious, metabolic, or toxic causes for liver disease. Subjects were further excluded if they experienced an "overlap" syndrome of AIH with primary biliary cirrhosis, primary sclerosing cholangitis, or chronic viral hepatitis (14). A data collection sheet was completed for all the patients. The medical records of all patients aged 0 to 19 years diagnosed with AIH or CCH between the years 1980 and 1998 were evaluated. Details of patients' growth and medical history, including gender, weight, ethnicity, and age at onset of symptoms, were recorded. Results from biochemical liver tests obtained at time of presentation to a referral center, including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and conjugated bilirubin, and prothrombin time, were also recorded. Serological markers (ANA, SMA, and LKM-1), and HLA type, when available, were noted as well. Liver biopsies were obtained at the time of presentation to a referral center, except for those from two patients who died awaiting OLT and from five patients who presented in fulminant hepatic failure. Children who were diagnosed with CCH were found to have classic histological findings (interface hepatitis, periportal fibrosis) on liver biopsy, hypergammaglobulineamia, and absent serological findings consistent with diagnoses of type 1 and type 2 AIH. Pharmacotherapy directed at AIH or CCH was recorded.

Liver failure and requirement for OLT are defined by the criteria set forth by the King's College Hospital, London (15). Recurrent disease is defined as the presence of autoantibodies (in patients with autoimmune hepatitis) at a titer >=1:40, elevated serum transaminases to at least three times the upper limit of normal, features of chronic hepatitis (portal inflammatory infiltration by mononuclear cells associated with interface hepatitis, or lobular inflammation associated with confluent or bridging fibrosis), need for increase in glucocorticoid dose, and lack of serum markers for viral hepatitis (16). Allograft rejection is alternatively defined histologically by mixed portal inflammation, eosinophils, endotheliitis, and bile duct damage and biochemically by the absence of autoantibodies (17,18). All patients who fulfilled the criteria for AIH and CCH who did not present in fulminant hepatic failure received immunosupression. Patients were considered to have responded to therapy if they achieved normalization of serum transaminases or liver histology (19).

Statistical Analysis

Continuous data is reported as mean±SEM. *P*-values for mean comparisons were computed using *t*-tests. *P*-values for comparing proportions were computed using chi-square methods.

RESULTS
Patient Characteristics

Sixty-five pediatric patients who were diagnosed with AIH or CCH between 1980 and 1998 met study inclusion criteria. Forty-one patients (63%) were female. Twenty-eight patients (43%) were Hispanic, 28 (43%) were Caucasian, 8 (12%) were African-American, and 1 (2%) was Asian. Forty-three patients (66%) were diagnosed with type 1 AIH, eight (12%) with type 2 AIH, and 14 (22%) with CCH. Females comprised 73% of the Caucasian patients, 53% of the Hispanic patients, and 62% of the African-American patients with AIH. Children with type 1 AIH, type 2 AIH, and CCH were diagnosed at median ages of 11, 5, and 9 years, respectively. A summary of patient population data is found in Table 1.

TABLE 1. Summary of patient population	
Total number of patients	65
Female patients	41 (63%)
Patients with type 1 AIH	43 (66%)
Patients with type 2 AIH	8 (12%)
Patients with CCH	14 (22%)
Median age at diagnosis for all patients	9 years, 8 months (range 4 months–19 years)
Median age at diagnosis for patients with type 1 AIH	11 years (range 2 months–18 years, 8 months)
Median age at diagnosis for patients with type 2 AIH	5 years (range 6 months–12 years)
Median age at diagnosis for patients with CCH	9 years (range 18 months–19 years)
Median follow-up period	8 years (range 3 months–18 years, 10 months)
Hispanic patients	43%
Caucasian patients	43%
African-American patients	12%
Asian patients	2%

AIH, autoimmune hepatitis; CCH = cryptogenic chronic hepatitis.

Table 1. Summary of patient populationAIH, autoimmune hepatitis; CCH = cryptogenic chronic hepatitis.

Laboratory Results at Time of Presentation to Referral Center

Mean ALT and AST (U/dL±SEM) were 411±77 and 402±70 for children who underwent OLT, compared with 916±199 and 844±156, respectively, for those who did not undergo OLT ($P < 0.05$). The mean total and conjugated bilirubin levels and prothrombin times were higher in children who underwent OLT when compared with those who did not undergo OLT. However, no statistically significant differences were found with regard to total bilirubin levels, conjugated bilirubin levels, or prothrombin times and the presence or absence of OLT (Table 2).

TABLE 2. Laboratory data at time of presentation to referral center			
Laboratory test	Patients receiving OLT	Patients not receiving OLT	P-value
	Mean value (±SEM)	Mean value (±SEM)	
ALT (U/dL)	411±77	916±199	<0.05[a]
AST (U/dL)	402±70	844±156	<0.05[a]
Total bilirubin (mg/dL)	11±2.0	7.5±1.5	0.21
Conjugated bilirubin (mg/dL)	7.8±2.0	4.2±0.9	0.11
Prothrombin time (seconds)	16.1±0.5	15.3±0.7	0.30

OLT, orthotopic liver transplant; ALT, serum alanine aminotransferase; AST, aspartate aminotransferase.
[a] P-values <0.05 are considered statistically significant.

Table 2. Laboratory data at time of presentation to referral centerOLT, orthotopic liver transplant; ALT, serum alanine aminotransferase; AST, aspartate aminotransferase.[a] P-values <0.05 are considered statistically significant.

OLT and Patient Outcome

Sixty-two patients (95%) with AIH or CCH received immunosuppressive therapy. Glucocorticoids were administered alone (with dose-reduction from 2 mg/kg per day of intravenous methylprednisolone or oral prednisone to 0.3 mg/kg per day of prednisone without discontinuation) or in combination with azathioprine (1–2 mg/kg per day) or 6-mercaptopurine (1–2 mg/kg per day). Seven (28%) of the nontransplanted patients had active disease at the end of the study period. The three (5%) patients who presented in fulminant hepatic failure were not treated with immunosupressive therapy and were immediately evaluated for OLT. Children who did not respond to immunosuppressive therapy were referred for OLT evaluation as well.

Seven patients (11%) died. Two of these patients died without being listed for transplantation (one refused transplant because of religious convictions and the other died acutely from rapid deterioration of chronic disease). The other five died posttransplantation. For the latter group, the median time from placement on the transplantation list to OLT was 37 days (range 2–128). There was evidence of medical noncompliance in one of the patients who died of hepatic failure (14%) and in none of the patients who survived.

At the end of the study period, 40 patients (62%) had undergone OLT. Nine (22.5%) of these patients received more than one transplant and 13 (33%) experienced disease recurrence. A significant relationship was found between type of autoimmune-associated liver disease and the presence or absence of OLT. Twenty-two (51%) of the patients with type 1 AIH, six (75%) with type 2 AIH, and 12 (86%) with CCH underwent OLT (P <0.05). Patients with CCH were more likely to receive an OLT than those with type 1 AIH (P =0.03). However, no significant difference was noted between type 1 and type 2 AIH (P =0.27) or between type 2 AIH and CCH (P =0.60) with regard to the need for OLT.

There was no significant relationship between disease type and recurrence after transplantation. Nine of the patients with type 1 AIH who underwent OLT (41%), two with type 2 AIH who underwent OLT (33%), and two with CCH who underwent OLT (17%) experienced disease recurrence posttransplantation (P =0.41). Four of the nine patients who underwent retransplantation had hepatic artery thrombosis in the early postoperative period and the other five died from complications of graft failure (four from complications of allograft rejection and one from overwhelming sepsis).

Ethnicity was not significantly related to the presence or absence of OLT. Eighteen of the Hispanic patients (64%), 14 of the Caucasian patients (50%), and 7 of the African-American patients (88%) underwent OLT (P =0.16). More specifically, although a larger percentage of African Americans required OLT than did Hispanic or Caucasian patients, this difference was not significant (P =0.41).

Four of the Hispanic patients who underwent OLT (22%), four of the Caucasian patients (29%), and five of the African American patients (71%) experienced disease recurrence posttransplantation. A trend toward a relationship between ethnicity and disease recurrence after OLT did exist (P =0.08). African-American children with AIH or CCH had a significantly higher rate of disease recurrence after OLT when compared with similar Hispanic patients (P =0.03) and a tendency toward a higher rate of disease recurrence when compared with similar Caucasian patients (P =0.08). There was no significant relationship between the rate of disease recurrence after OLT for Hispanic and Caucasian patients after OLT for AIH or CCH (P =0.49).

DISCUSSION

A higher percentage of our study population required liver transplantation for AIH than had previously been reported in children from other referral centers. In 1993, Maggiore et al. found that, of 31 children diagnosed with type 1 AIH, two patients died of liver failure and five ultimately underwent OLT after a mean follow-up period of approximately 5 years [20]. In 1997, Gregorio et al. reported on the 20-year experience of 52 children referred to the Pediatric Liver Unit of King's College Hospital for evaluation and treatment of type 1 and type 2 AIH [8]. These researchers found that, of their patients, followed for a median period of 5 years, nine required OLT and one died from fulminant hepatic failure while awaiting OLT. In comparison, 51% of our group of patients with type 1 AIH (43 subjects) and 55% of those with either type 1 or type 2 AIH (51 subjects) required transplantation. Because our patients were followed for a relatively long median time of 8 years, the data suggest that the need for transplantation continues over time. An even higher proportion of children in our study group with CCH underwent OLT. One should, however, extrapolate from these data cautiously, because the rates determined represent those of large pediatric referral centers; those representing the general population may be significantly lower.

Those patients who underwent OLT had significantly lower serum transaminase levels at time of presentation to a referral center than did those who did not undergo transplantation. Although these findings are unlikely to represent "liver burnout" in the former group, they do encourage further evaluation of serum transaminases as prognostic indicators in patients with AIH and CCH. Interestingly, no significant differences in the extent of cholestasis, as represented by total and conjugated serum bilirubin levels, or coagulopathy, as represented by prothrombin times, were found between the two groups upon referral.

The need for OLT was related to the type of autoimmune-associated liver disease diagnosed in our patient population. In a direct comparison, a significantly higher proportion of patients with CCH received liver transplants than did patients with type 1 AIH. This finding may further distinguish CCH as a virulent disease entity. However, no other direct comparison of disease type and the presence or absence of OLT was found to be significant.

Of note, the need for retransplantation and the presence of hepatic artery thrombosis in our series were representative of those values seen in the overall pediatric OLT population at UCLA. Twenty-two and a half percent of patients in the current study underwent retransplantation and 10.0% experienced hepatic artery thrombosis of the transplanted graft. Similarly, Goss et al. recently reported that, of 440 consecutive pediatric patients undergoing OLT at UCLA, 22.0% required retransplantation and 12.5% experienced hepatic artery thrombosis (21).

Our study confirms a high rate of disease recurrence among children undergoing OLT for AIH. In 1997, Birnbaum et al. evaluated the presence of disease recurrence in six children after OLT for AIH. Of the six, five experienced disease recurrence at a mean time of less than a year and three required retransplantation (10). These data complement those compiled by Gotz et al., who found a disease recurrence rate of 55% in 22 primarily adult patients followed for a mean of 47 months, and Prados et al., who determined a disease recurrence risk of 68% at 5 years among 27 such patients (22,23). None of the seven patients in the latter study who underwent OLT for type 2 AIH experienced disease recurrence posttransplantation (P =0.059). Interestingly, two of the six patients in our study with type 2 AIH experienced disease recurrence after OLT, but, again, no significant relationship was found between disease type and recurrence posttransplantation. We also report moderate disease recurrence in children undergoing OLT for CCH.

Little information exists with respect to the role of patient ethnicity on the outcome of patients with AIH or CCH. No significant relationship was found between ethnicity and the presence or absence of OLT among the children in our report. However, our study does suggest a relationship between ethnicity and disease recurrence after OLT. The African-American patients experienced significantly more-frequent disease recurrence posttransplantation than did Hispanic patients and a trend toward more-frequent disease recurrence than did Caucasian patients.

The study has several limitations. First, because the study period spans 19 years, it involves the pre–Hepatitis C virus-testing era. Indeed seven (11%) of the patients in the current report were not tested for the presence of Hepatitis C antibody. Additionally, several studies have suggested an association between Hepatitis C viral infection with the presence of LKM-1 antibody (24,25). Therefore, several of our patients, especially those with type 2 AIH, may be inappropriately included in the study population. Second, only three (5%) of the patients examined in our study underwent HLA testing. Because differing HLA markers are found between ethnic groups in patients with other autoimmune disorders, such as systemic lupus erythermatosus (26), these data may more accurately characterize disease progression based on genetically determined differences in patients with AIH. Finally, over the last several years, promising additional drug options have become available for use in patients with glucocorticoid and azathioprine-refractory autoimmune hepatitis, including cyclosporine (27–29), tacrolimus (30), methotrexate (31), ursodeoxycholic acid (32), cyclophosphamide (33), and mycophenolate mofetil (34). Thus, the overall need for OLT in patients with AIH may actually decline with the increasing use of these and other drugs. Future prospective, multivariate analyses, incorporating both HLA testing and drug trials, are needed to further elucidate these complex disease processes. Because of the infrequency of diagnoses of autoimmune-associated liver diseases in children, a mulitcenter approach to these studies is advocated.

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Table 2

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