CLINICAL AND BIOCHEMICAL FEATURES OF AUTOIMMUNE HEPATITIS IN 36 PEDIATRIC PATIENTS

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ABSTRACT - ***Background*** **-** Few studies on autoimmune hepatitis have enrolled non-Caucasian groups. ***Aims*** **-** To evaluate Brazilian children with type 1 and 2 autoimmune hepatitis regarding outcome and clinical and biochemical parameters. ***Patients and Methods*** - Thirty-six patients were submitted to a protocol that evaluated the clinical history, physical and biochemical data, and the course of the disease. Twenty-four children had type 1 autoimmune hepatitis, seven had type 2 and five had unclassified autoimmune hepatitis. Most patients were females (77%), with a median age at diagnosis of 11 years, and the median duration of symptoms was 5.5 and 8 months for types 1 and 2, respectively. Jaundice and choluria were the most common clinical manifestations. ***Results*** - Treatment with azathioprine and prednisone was successful in patients with type 1 and 2 autoimmune hepatitis. AST and ALT decreased after 4 to 8 weeks of treatment compared to pretreatment levels in type 1 autoimmune hepatitis. Increased GGT values returned to pretreatment levels after 1 year in the two types. Three patients died and three other patients underwent liver transplantation. ***Conclusions*** - Non-Caucasian children had a similar disease when compared to Caucasian ones with autoimmune hepatitis. Increased levels of GGT during the first year of treatment should not be the only parameter for the indication of cholangiopathy.

HEADINGS - Hepatitis, autoimmune. Gamma-glutamyltransferase. Child.

INTRODUCTION

Autoimmune hepatitis (AIH) is an inflammatory liver disease which is characterized by dense lymphomonocytic infiltration in the portal tract and liver-specific autoantibodies in the absence of any other known etiology. Additionally, the course of AIH is favorable when treated with immunosuppressors[33].

There are two types of AIH: type 1 AIH is recognized by the presence of smooth muscle antibodies (SMA) and/or antinuclear antibodies (ANA), and type 2 is characterized by the presence of anti-liver/kidney microsome type 1 antibodies (LKM-1)[16, 20]. Recently, STRASSBURG and MANNS[30] proposed a third type whose marker is soluble liver antigen/liver pancreas antigen (SLA/LP). Other reported markers that are considered to be relevant for the diagnosis of AIH are: hepatic asialoglycoprotein receptor (ASGP-R), liver-specific cytosolic antigen (LC1), glycosphingolipid (sulfatide), antineutrophilic cytoplasmic antibodies (pANCA), and the anti-actin antibody[21]. In a previously reported series, autoantibodies were absent in approximately 10%-20% of cases and the patients presented a good outcome with corticotherapy[22].

Variant overlap syndromes have been described, including the overlap syndrome of AIH and primary biliary cirrhosis in adults, and AIH associated with sclerosing cholangitis in adults and children[4, 7, 14, 28]. Since the wide diversity of clinical and biochemical parameters involved in this disease makes its diagnosis difficult, the International Autoimmune Hepatitis Group[1] has defined guidelines to establish the diagnosis of AIH based on clinical and biochemical criteria. The sensitivity of these criteria ranges from 97% to 100% and their specificity is at least 89.8%[1, 3, 17].

Type 1 AIH presents two peaks of incidence, one between 10 and 20 years of age and a second one between 45 and up to 70 years of age. Type AIH 1 is a relatively benign disease. Type 2 occurs in infancy, is more severe, and progression to cirrhosis is more frequent, irrespective of immunosuppressant treatment[16, 20]. However, an

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important study conducted on children found no differences between types 1 and 2 regarding severity of the disease or long-term follow-up findings[15].

The objective of the present study was to evaluate and compare pediatric patients with type 1 and 2 AIH, as well as cases of unclassified AIH, regarding clinical and biochemical parameters and the course of the disease.

PATIENTS AND METHODS

Thirty-six patients aged 1 to 18 years were admitted to the Hepatology Pediatric Outpatient Clinic of the University Hospital, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, SP, Brazil, between August 1991 and September 2003. The diagnosis on admission was AIH and was confirmed based on the scoring system of the International Autoimmune Hepatitis Group[1]. Scores for a definite diagnosis were obtained for 23 patients (64%), while 13 (36%) were diagnosed as probably positive. A research protocol was applied prospectively to 23 patients and retrospectively to 13 patients who were analyzed by reviewing their records. The study was approved by the Institutional Review Board of the Faculty of Medical Sciences - UNICAMP.

For the purpose of this study, patients were divided into three groups: group 1 consisted of patients with type 1 AIH, group 2 of patients with type 2 AIH, and group 3 of patients whose disease had not been classified. The following variables were evaluated: sex, age, skin color, time from the first symptoms to diagnosis, more frequent complaints, duration of follow-up care at our Health Service, nutritional status, and presence of hepatomegaly and splenomegaly. Levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), albumin, gamma-globulin and International Normalized Prothrombin ratio (INR) were determined before treatment (baseline) and after 4 to 8 weeks of immunosuppressant therapy (disease course). Gamma-glutamyltransferase (GGT) was evaluated at four different periods: before therapy (T1), from the 4th to the 8th week (T2), 6 months after first evaluation (T3), and 1 year after treatment (T4). A liver biopsy specimen was available for all patients. The histological findings were compatible with AIH in 32 patients, and four patients had cirrhosis.

Weight and height of the patients were measured with appropriate instruments during an outpatient visit prior to treatment. Reference tables from the National Center for Health Statistics[24] were used as reference values for height and weight. Data were classified by weight-for-age, height-for-age and body mass index (BMI) according to the number of standard deviations of these indicators from the reference values (Z-score)[12].

Treatment consisted of prednisone, 1-2 mg/kg/day, up to a maximum dose of 60 mg/day, and azathioprine, 1-2 mg/kg/day, up to a maximum dose of 75 mg. After 1-2 months of therapy, prednisone was gradually reduced according to response. Response to therapy was classified according to previously published criteria[17].

Statistical analysis

Frequency tables were used in the analysis of categorical variables and descriptive statistics was applied to continuous variables. Categorical variables were compared between groups by Fisher's exact test[13]. The nonparametric Kruskal-Wallis test was used to compare continuous variables between groups. The multiple comparisons test was applied when a statistically significant difference was detected[18]. The Mann-Whitney exact test was used to analyze longitudinal variables after exclusion of data from Group 3[29]. Wilcoxon's test for related or paired measurements was used separately for groups 1 and 2 to compare measurements obtained at baseline and during the course of the disease[5].

GGT values at T1, T2, T3 and T4 were compared separately for groups 1 and 2 using Friedman's test for related or paired measurements[5]. Differences were tested in pairs (T1 x T2; T1 x T3, T1 x T4; T2 x T3; T2 x T4, T3 x T4).

Significance was established at $P \leq 0.05$ in all tests.

RESULTS

Of the 36 children enrolled in this study, 24 were diagnosed as having type 1 AIH (group 1), 7 had type 2 (group 2) and 5 had unclassified AIH (group 3). Of the five cases that were not classified, three tested negative for autoantibodies, one tested positive for parietal cell antibody and one for antibody to liver-specific cytosolic antigen. One patient classified as type 2 also tested positive for anti-mitochondria antibody (1:320) but histology was compatible with AIH.

With respect to skin color, in group 1, 12 patients were white, 4 were black and 8 were mulattos; in group 2, six patients were white and one was of Asian origin, and in group 3, two were white and three were mulattos.

Table 1 shows the clinical features of AIH patients in groups 1, 2 and 3 at baseline. There was a statistically significant difference between groups with respect to the Z-score for height when group 1 was compared with group 2, with a higher Z-score in group 2.

TABLE 1 – Clinical features of patients with type 1 autoimmune hepatitis (AIH) (group 1), type 2 AIH (group 2) and unclassified AIH (group 3) at baseline

Variables	Group 1 (n = 24)	Group 2 (n = 7)	Group 3 (n = 5)	*P* values
Gender, female/male	17/7	6/1	5/0	0.3035
Median age at diagnosis (years)	11	3.7	11.02	0.3470
Median duration of symptoms (months)	5.52	8.05	4.01	0.3470
Median time of follow-up (months)	46.67	46.78	46.88	0.9428
Median Z-score for weight	-0.22	0.57	0.52	0.0763
Median Z-score for height	-0.27	1.20	1.04	**0.02**
Median Z-score for BMI	0.10	-0.33	0.21	0.5106
Jaundice	14	6	5	0.3571
Choluria	11	2	1	
Abdominal pain	4	2	1	
Fulminant liver failure		1		
Hepatomegaly	20	6	4	1.0
Splenomegaly	20	6	3	1.0

No significant differences in laboratory parameters were observed between groups 1 and 2 at baseline (Table 2).

TABLE 2 – Comparison of baseline biochemical data between children with type 1 (group 1) and type 2 autoimmune hepatitis (group 2)

Variables	Group 1	Group 2	*P* values
ALT (U/L)	323.0	201.0	0.2380
AST (U/L)	723.5	290.0	0.2632
AP (U/L)	830.0	844.5	0.3303
Gamma-globulin (g/dL)	3.28	2.68	0.2246
Albumin (g/dL)	3.03	3.57	0.1628
INR	1.64	1.78	0.6466

Data are reported as median

Comparing baseline and treatment values, a decrease in the levels of liver enzymes, INR and gamma-globulin was noted, as well as an increase in albumin levels. However, at 4 to 8 weeks, these results were statistically significant only for patients of group 1 (Table 3).

TABLE 3 – Statistical comparison of liver enzymes (AST, ALT and AP), gamma-globulin, albumin and INR at baseline and during the course of the disease between patients with type 1 (group 1) and type 2 autoimmune hepatitis (group 2)

Biochemical parameters	*P* value Group 1 (n = 24)	*P* value Group 2 (n = 7)
AST	0.0001	0.0625
ALT	0.0001	0.0625
AP	0.0002	0.0625
Gamma-globulin	0.0005	0.1250
Albumin	0.025	0.8125
INR	0.0084	0.0625

GGT levels were measured at all time intervals in only 20 patients (15 patients of group 1 and 5 of group 2). A significant difference was only observed between T3 and T4 in group 1 ($P = 0.0250$) and between T3 and T4 ($P = 0.0180$) in group 2 (Figure 1).

The clinical outcome of the patients studied is shown in Table 4.

Retrograde endoscopic cholangiopancreatography was carried out in four patients who showed persistently high levels of GGT. The results were normal in three patients, but one patient showed alterations compatible with liver cirrhosis.

Thirty-five patients underwent treatment. One patient had fulminant hepatic failure and died before she could receive immunosuppressive therapy. The response of the patients to treatment is shown in Table 5.

DISCUSSION

AIH is a chronic disease that affects all ages and ethnic groups. Pediatric patients, however, present distinct clinical features compared to adults and the outcome is also different in this group. This variability represents a diagnostic challenge.

Most studies on AIH in infancy have been performed on Caucasian populations. Few studies have enrolled non-Caucasian groups, showing differences in the clinical features

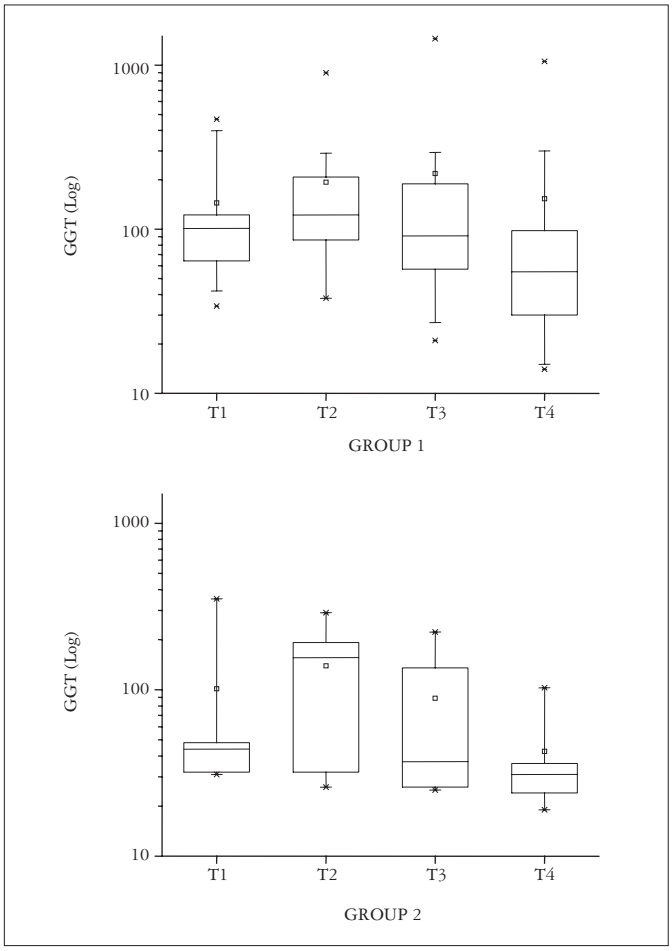

FIGURE 1 – GGT levels (on a logarithmic scale) in patients from groups 1 and 2 at four follow-up periods: T1 (diagnosis), T2 (4 to 8 weeks of treatment), T3 (6 months after treatment), and T4 (one year after treatment). Data are presented as box-plots

TABLE 4 – Clinical course and associated diseases in patients with type 1 autoimmune hepatitis (AIH) (group 1), patients with type 2 AIH (group 2) and patients whose disease had not been classified (group 3)

Variables	Group 1	Group 2	Group 3
Death	1	2	0
Liver transplant	3	0	0
Pancytopenia due to azathioprine	1	1	0
Persistent vomiting due to azathioprine	0	1	0
Need to use cyclosporin	2	2	0
Diabetes mellitus	2	0	0
Hypothyroidism	1	0	1
Vasculitis	1	0	0
Megaloblastic anemia	1	0	0

of the disease. In a retrospective study, ZOLFINO et al.[34], comparing 12 non-Caucasian patients with 180 Caucasian-European patients, observed that non-Caucasian patients were younger, presented more biliary and cholestatic alterations, and responded poorly to standard immunosuppressant therapy.

TABLE 5 – Response to immunosuppressant treatment in patients with type 1 autoimmune hepatitis (AIH) (group 1), patients with type 2 AIH (group 2) and patients whose disease had not been classified (group 3)

Variables	Group 1 (n = 24)	Group 2 (n = 6)	Group 3 (n = 5)
Complete response	14	4	4
Partial response	3	0	0
No response	1	0	0
Treatment failure	6	0	0
Relapse	0	2	1

Another study comparing 115 Brazilian adult and pediatric patients with North American/Caucasian patients showed that Brazilian patients were younger and had a lower incidence of other simultaneous autoimmune diseases[9].

In the present study, patients showed a wide ethnic diversity, females were more frequent and the median age of the patients was 11 years, in agreement with the results reported by GREGORIO et al.[15]. There was no significant difference between groups with respect to age at diagnosis but patients in group 2 tended to be younger, in agreement with literature data[15, 26].

No difference in the interval between the onset of symptoms and diagnosis was observed between groups. The median period in groups 1 and 3 was less than 6 months, indicating that a 6-month duration of disease symptoms is not adequate for defining chronicity, as reported by other authors who demonstrated histological features of chronic hepatitis even in children with a symptom duration of less than 6 months[15, 19, 32]. In addition, the period from the onset of symptoms to the diagnosis should not hinder the investigation of AIH because in a small percentage of patients disease manifestation is acute, including the manifestation of histological parameters[15]. The median interval between the onset of symptoms and diagnosis was 5.5 and 8.0 months in groups 1 and 2, respectively. GREGORIO et al.[15] reported a shorter interval (1 and 1.8 months). These differences may reflect the current situation in Brazil in which delays in referral to a specialized center are frequent.

Patients presented good nutritional status at the time of diagnosis, as demonstrated by the Z-scores for weight, height and BMI, in agreement with published data[6]. However, there was a significant difference in the Z-score for height, with group 2 patients being taller than group 1 children.

Jaundice was observed in 69.4% of patients and choluria in 38.8%. Some patients had only subtle nonspecific symptoms or had been referred because of an increase in aminotransferase levels. GREGORIO et al.[15] reported the occurrence of acute symptoms, similar to viral hepatitis, in over 50% of patients.

Fulminant hepatic failure was observed in one patient of group 2 which resulted in her death. Some cases of type 2 AIH presenting as fulminant hepatic failure in infancy have been reported in the literature[6, 15, 21, 23, 25].

Two patients with type 1 AIH had insulin-dependent diabetes mellitus. GREGORIO et al.[15] found 7 diabetic patients in a study of 52 pediatric patients (3 with type 1 AIH and 4 with type 2). PORTA[26] described two cases of diabetes in patients with type 2 AIH in a group of 47 children. Da SILVA et al.[10] observed a high frequency of anti-islet and anti-insulin antibodies in patients with AIH; however, only few of them progressed to diabetes mellitus. CZAJA et al.[9] reported 2 diabetic patients among 161 patients from the United States, 157 of them being older than 18 years, and no diabetic patient among 115 Brazilian adults and children.

Group 1 patients responded to immunosuppressive therapy as indicated by the significant reduction in serum AST and ALT levels. No significant differences were observed for group 2 patients ($P = 0.0625$), a finding that might be attributed to the small number of patients with type 2 AIH, or may indicate that a longer therapy is needed in order to achieve a significant reduction in this group. A marked reduction in aminotransferases was also observed by GREGORIO et al.[15] after 1 to 3 months of treatment.

Treatment with azathioprine was discontinued in one patient because of persistent vomiting and in two others because of pancytopenia. In these cases, cyclosporin was introduced. Standard maintenance therapy for all forms of AIH is defined in the literature as the combination of low doses of prednisone and azathioprine, which reduces the incidence of side effects caused by the corticoid[9, 31].

Cyclosporin has been used as a good alternative in cases of intolerance to conventional therapy[2, 11]. In our series, only four patients used cyclosporin: one died due to pneumonia after 4 months of treatment before reaching normal aminotransferase levels, two patients showed a good response to this treatment, and the remaining patient will require a longer evaluation in order to define his outcome.

The increase in albumin levels and decrease in INR and gamma-globulin levels during treatment reflected a significant improvement in group 1 patients, demonstrating recovery of liver synthesis function and a reduction in the inflammatory process due to immunosuppressive treatment.

An increase in GGT levels was observed during treatment; however, levels returned to pretreatment values at the end of 1 year. There is no report in the medical literature regarding changes in GGT levels with the medication used in this treatment. This finding is important and should be confirmed in other series since it might postpone the investigation of autoimmune cholangitis by endoscopic retrograde cholangiography or magnetic resonance cholangiography until 1 year after the beginning of treatment.

It is important to emphasize that the variant overlap syndromes represent a challenge in the diagnosis of AIH[8, 14]. CZAJA[7] defines AIH and primary biliary cirrhosis, and AIH and primary sclerosing cholangitis as overlap syndromes, while autoimmune cholangitis and autoimmune hepatitis with negative antibodies are classified as outlier syndromes. In the present series, magnetic resonance cholangiography and endoscopic retrograde cholangiopancreatography ruled out the possibility of sclerosing cholangitis, and the patients in the unclassified group had a score compatible with a definite diagnosis according to the scoring system of the International Autoimmune Hepatitis Group[1].

Complete response to treatment was observed in 22 of 35 patients who received adequate therapy (62.8%). PORTA[26] reported a complete response for 61% of 36 children. The median follow-up time in the referred clinic was 4 years and there were three deaths during this period: two in group 2 (one due to fulminant hepatic failure and one due to pneumonia) and

one in group 1 (due to postoperative complications following liver transplantation). Only three patients underwent a liver transplantation, corresponding to less than 10% of cases. This percentage is similar to published data[15, 27].

In conclusion, the clinical and laboratory parameters obtained for the multiracial patients included in this study, as well as the manifestations of the disease, are in agreement with data published in international studies carried out on Caucasian patients.

Bellomo-Brandão MA, Costa-Pinto EAL, De Tommaso AMA, Hessel G. Características clínicas e bioquímicas da hepatite autoimune em 36 pacientes pediátricos. Arq Gastroenterol. 2006;43(1):45-9.

RESUMO – ***Racional*** **-** Poucos estudos sobre hepatite autoimune têm sido conduzidos em pacientes não-caucasianos. ***Objetivos*** **-** Avaliar crianças brasileiras com hepatite autoimune tipos 1 e 2 em relação à evolução clínica e parâmetros clínicos e bioquímicos. ***Métodos*** - Trinta e seis pacientes foram incluídos em um protocolo que registrou os dados da história clínica, exame físico, dados bioquímicos e evolução da doença. Vinte e quatro crianças tinham hepatite autoimune tipo 1, sete pacientes hepatite autoimune tipo 2 e em cinco casos, a hepatite autoimune não pôde ser classificada. A maioria dos pacientes pertencia ao sexo feminino (77%), a mediana de idade ao diagnóstico foi de 11 anos e a mediana de duração dos sintomas foi de 5,5 e 8 meses, para os tipos 1 e 2, respectivamente. Icterícia e colúria foram as manifestações clínicas mais freqüentes. ***Resultados*** - A terapia com azatioprina e prednisona foi eficaz para os pacientes com os tipos 1 ou 2 de hepatite. As enzimas AST e ALT apresentaram decréscimo em relação aos valores no diagnóstico, após 4 a 8 semanas de tratamento, nos pacientes com hepatite autoimune do tipo 1. Os valores de GGT tornaram-se mais elevados após o início da terapia e retornaram aos níveis pré-tratamento após 1 ano, nos dois tipos de hepatite. Três pacientes foram a óbito e outros três realizaram transplante hepático. ***Conclusões*** - Crianças não-caucasianas apresentaram doença semelhante a pacientes caucasianos com hepatite autoimune. Níveis elevados de GGT no primeiro ano de tratamento não devem ser o único marcador da existência de colangiopatia.

DESCRITORES - Hepatite auto-imune. Gama-glutamiltransferase. Criança.

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