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Original Article

Autoimmune-type chronic active hepatitis in children. A report of 23 cases at a Hospital in Northwestern Mexico

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Abstract

Introduction: Autoimmune type chronic active hepatitis (AI-CAH) is a rare pediatric disorder whose principal characteristics include hepatocellular dysfunction and active tissue damage with evolution to cirrhosis in 25–30% of cases. **Objective:** Our aim was to ascertain the evolution of 23 children with AI-CAH treated between 1978 and 2004 at the Hospital Infantil del Estado de Sonora in the Sonora State capital of Hermosillo in northern Mexico. **Materials and methods:** We conducted a retrospective review that included the following variables: age; sex; personal antecedents; signs and symptoms; laboratory and medical office studies; histologic tissue pattern obtained by biopsy; treatment; evolution, and mortality. **Results:** Thirteen males and 10 females participated in the study; predominant signs were hyporexia, fatigue-hepatomegalia, and icterus. Ten patients presented moderate anemia and six patients, leukopenia and thrombocytopenia. Eighteen patients presented hypergammaglobulinemia. Twenty three patients had percutaneous (p.c.) liver biopsy, and we observed the following histologic pattern: rupture of the limiting

plate; necrotic foci; cholangiolar proliferation, and fibrotic bridges; in addition, four patients demonstrated precirrhotic changes. Twenty one children received prednisone for periods of between 1 and 12 years; in seven cases, children were administered azathioprine. Six children presented histologic, biochemical, and clinical remission, nine experienced biochemical remission but presented inflammatory activity, five abandoned treatment, and three died due to cirrhosis, liver insufficiency, and other complications. **Discussion:** To date, AI-CAH etiology continues to be unknown, while treatment has not been importantly modified in 50 years and continues to consist of prednisone alone or in association with azathioprine.

Key words: Autoimmune hepatitis, autoimmune-type chronic active hepatitis.

Introduction

Autoimmune hepatitis (AI-CAH) is a rare liver disorder of unknown etiology. It is inflammatory in nature and can evolve in a chronic and eventually an instantly fatal manner. Its clinical manifestations are syndromatic and the disease is occasionally asymptomatic; AI-CAH implies hepatocellular dysfunction with tissue destruction that can evolve into cirrhosis. AI-CAH has been accepted as a disease possessing autoimmunity phenomena¹ with two variants described: type I, with antinuclear antibodies and anti-smooth muscle, and type II, with antimicrosomal antibodies for liver and kidney with other associated antibodies²⁻⁵ (Table I).

On the other hand, a group of pediatric patients did not demonstrate defined immunologic-change patterns.²⁻⁵ Diagnosis is established excluding chronic viral hepatitis and those related with metabolic disorders; histologically, there is accumulation of lymphocyte and plasmatic cells in porta spaces and necrotic foci in hepatic lobules, and rupture of the portal pathway-adjacent limiting plate, extending the inflammatory reaction to parenchyma.^{4,5} Treatment is based on use of prednisone- and azathio-

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Table I. Autoimmune-type active chronic hepatitis. Classification according to circulating antibody type at pediatric ages.²⁻⁵

Findings	Type 1	Type 2
Average age (years)	10	< 6
Characteristic antibodies	ANA, SMA	Anti-LMK1
Associated antibodies	P-ANCA, A-ASGPR, SLA/LP, Ac-ASCA) antibodies, ANA	Anti-liver cytosol (anti-LC1), identified as forminotransferase cyclodeaminase, Anti LKM1
Associated autoimmune diseases	Ulcerative colitis, sclerotizing cholangitis, arthritis, vasculitis	Polyendocrinopathy, vitiligo, alopecia, diabetes mellitus, thyroiditis
Characteristic histologic changes, negative immunologic markers**	Until appearance of markers	Until appearance of markers
Genetic alleles*	DRB1* 03001 DRB1* 04001 DRB1* 1501 DRB1* 04004 DRB1* 0405 DRB1* 1301	HLA-B14 HLA-DR3 HLA-DRB*7
Clinical form	69%, early-stage cirrhosis	In children < 5 years of age, 50–60% severe, some fulminant, 30% early cirrhosis

* Genetic Allelic; **responds to immunosuppressor treatment. ANA, Antinuclear antibodies; SMA, anti -smooth muscle antibodies, Anti-LMK1, Anti-Liver and Kidney microsome antibodies; P-ANCA, perinuclear anti-cytoplasmic antibodies; A-ASGPR, antisialoglycoprotein receptor antibody; SLA/LP, soluble liver antigen/liver pancreas antigen; Ac-ASCA, antichromatin anti-*Saccharomyces cerevisiae*.

prine-type and other immunosuppressors; cyclosporine, rapamycin tacrolimus, micophenolate mofetil, deflazacort, budesonide, ursodeoxycholic acid, cyclophosphamide, 6 mercaptopurine, and liver transplant have also been utilized.⁵⁻⁹ In this work, we present the evolution followed in 23 patients treated at a Mexican Health System (SSA) secondary healthcare-level hospital in northern Mexico.

Materials and methods

We retrospectively reviewed patient files at the Hospital Infantil del Estado de Sonora (Sonora State Children Hospital in Hermosillo, Sonora, Mexico) of children seen at the Hospital from January 1978 to December 2004, and considered the following variables: age; sex; personal antecedents; time from disease initiation prior to hospital admission; disease signs and symptoms; laboratory studies; liver biopsy with histologic pattern; evolution, and mortality.

Results

Twenty three patients were included in the study of both sexes: nine females and 14 males. In two cases, ages ranged from 2–6 months, from 1–2 years in eight children, from 3–6 years in eight patients, from 7–11 years in two patients, and from 12–14 years in three children.

With regard to personal antecedents, we reviewed the following: 16 cases had been diagnosed with liver disease; in seven cases, the sole datum was hepatomegaly. Among all participating children, three had an antecedent of having received diphenylhydantoin- and fenobarbital-type anticonvulsants, two patients had at some moment of disease evolution a laboratory determination of a positive test for cytomegalovirus, and one child was positive for infectious mononucleosis.

Disease evolution time prior to hospital admission was referred as 1–2 months in four children, from 3–6 months in 11 children, and between 6 months and 1 year in eight patients. Predominant referred signs and symptoms included hyporexia, fatigue, hepatomegaly, and icterus, as shown in *Table II*.

With respect to laboratory studies, 10 children exhibited hemoglobin < 10 g/dL, six demonstrated leukocytes < 3,000 x mm³, six showed platelets < 100,000 x mm³, 13 children had elevated direct bilirubin between 2 and 15 mg/dL, and all children showed elevation of alanine aminotransferase (ALT), aminoaspartate transferase (AST), and glutamic-pyruvic transferase (GPT). In 18 patients, findings included the following: elevated gammaglobulins; bile-duct pigments were positive in five patients, and 18 children were submitted to the following studies: antinuclear antibodies; anti smooth-muscle antibodies; antimitochondrial antibodies; erythematous lupus cell (ELC); alpha-1 antitrypsin; the Venereal Disease Research Laboratory (VDRL) test for syphilis, and seric immunoglobulins. Only one child was positive for antimitochondrial antibodies (AMA), while two were positive for antinuclear antibodies (ANA). Serologic tests for hepatitis A, B, C

Table II. Signs and symptoms in 23 children with autoimmune chronic active hepatitis

Signs and symptoms	N (cases)	Proportion
Hyporexia	20	0.86
Hepatomegaly > 5 cm	20	0.86
Fatigue	18	0.78
Icteria	14	0.60
Hepatosplenomegaly	10	0.43
Ascitis	2	0.08
Arthralgas	2	0.08

were negative in 20 children; testing for hepatitis B was conducted only in five children because at the time of the study complete laboratory parameters were not available. With respect to imaging studies, ultrasound (US) was done in six children with hepatomegalia during the study phase; no categoric imaging of liver lesion was observed. All patients had percutaneous (p.c.) hepatic biopsy with Vin-Silverman needle. The histologic pattern included rupture of limiting plate with necrotic foci, cholangiolar proliferation, and fibrotic bridges; in addition, four patients demonstrated precirrhotic changes.

The Knodell scoring system^{10,11} was used in nine patients for appraising degree of hepatic tissue damage and in specimens of subsequent biopsies for evaluating treatment response. The following indicators were taken into consideration: periportal necrosis; degeneration and focal necrosis, and portal inflammation, which were classified according to the method described by the author. Three biopsies per patient were conducted—depending on time of disease evolution—and were effected at intervals of between 6 months and 1 year: in two patients with more control time (10 and 12 years), one had seven and the other, nine biopsies.

In treatment of the 23 children, drug used in 21 of these was prednisone at a initial dose of 2 mg/kg/day, not exceeding 60 mg/day, sustaining this dosage for at least 4–6 weeks and then reducing it to 1 mg/kg/day during 3 additional weeks. Additionally, according to transaminase levels we sustained a daily dosage of between 10 and 20 miligrams depending on patient age and weight. Of the same group of 21 children, three abandoned treatment very early, seven required a 1 mg/kg/day dose of azathioprine to control persistent high levels of control, while another three patients had their treatment suspended for 6–12-week periods, restarting treatment as soon as transaminase elevation was observed, as well as clinical signs of hyporexia, fatigue, and arthralgias. In two cases, one patient had fulminant hepatitis, was unable to initiate with immunosuppressive therapy, and died, transaminases maintaining an average daily dose of 25 mg.

According to biochemical remission criteria in children with long disease evolution, we used minimal prednisone doses of 5–10 mg daily and 12.5 mg of azathioprine; 13 children with good treatment response only 6, have their medication suspended due to clinical, biochemical, and histologic criteria. Nonetheless, they a 2-month-old patient in whom in principle prednisone use was unacceptable, abandoning subsequent controls.

Disease evolution

Six patients remained in clinical, biochemical, and histologic remission during 8 years, attending out-patient hospital consultations. Nine continue in biochemical and histologic remission, with favorable histologic changes according to the Knodell scale. One of these patients has

been in treatment for 12 years, with periods of medication suppression from 6–12 weeks; this patient has developed type 1 diabetes mellitus and has been insulin-dependent for the last 18 months. Another patient relapsed after 11 years without drugs and is at present in remission with use of prednisone, while five patients abandoned treatment.

In the 10 children aged > 3 years, the following occurred: three patients evolved to cirrhosis; of these, all abandoned treatment prior to 3 months and none returned for out-patient consultations; among another three children aged 3 years, one patient after 2 months of treatment showed data of precirrhosis and went to another institution for treatment, while two children continued with prednisone treatment, attended control appointments, and are now 5 years of age. These patients have had two biopsies each and have shown improvement. The remaining patient was on control with prednisone and suspended this treatment after 3 years; three biopsies were carried out, the latter two demonstrating histologic data of remission. Subsequently, this child moved to another city.

Among four patients aged < 18 months of age, one 2-month-old breast-feeding infant failed to attend a control appointment at 1 year of diagnosis and one 6-month-old child experienced rapid evolution and did not attend control appointments subsequently, while the remaining two patients continued in treatment with 6 and 12 years of follow-up, respectively, have received intermittent prednisone treatment, and are at present experiencing good evolution.

Of this series, the three patients who registered deaths presented cirrhosis, deaths, liver insufficiency, hemorrhage, and infections; one presented, in addition, aplastic anemia, which we did not relate with treatment because the patient had only received prednisone (*Table III*).

Discussion

AI-CAH is a rare disease with unknown etiology in which an immunologic background is recognized in liver damage evolution.^{1–5} Two variants have been identified according to the described pattern of positive circulating antibodies: type I (antinuclear and anti smooth-muscle antibodies), and type II (hepatic and renal antimicrosomal

Table III. Disease evolution in 23 children with autoimmune chronic active hepatitis.

Ages	Improvement	Cirrhosis	Deaths	Abandoned treatment
2–18 months	2	1	1	2*
2–3 years	2	4	-	3*
4–6 years	6	-	-	
7–11 years	1	1	1	
12–14 years	2	1	1	
Total	13 (0.56)	7 (0.30)	3 (0.13)	5*

* Patients who experienced rapid evolution to cirrhosis.

antibodies). In addition, other associated autoantibodies have been described, such as perinuclear anti-neutrophilic antibody (P-ANCA), antiasialoglycoprotein receptor antibody (A-ASGPR), soluble liver antigen/liver pancreas antigen (SLA/LP), antichromatin and anti-*Saccharomyces cerevisiae* antibodies (Ac-ASCA) for type I and for type II, and anti-liver cytosol I (Ac-LCI) antibodies. Other autoimmune illnesses have also been associated with AI-CAH, such as ulcerative colitis, sclerotic cholangitis, arthritis, polyendocrinopathic vasculitis, vitiligo, diabetes mellitus, and thyroiditis, as demonstrated in *Table I*.²⁻⁵

In this series, it was impossible to catalog patients within a specific known classification. In three cases, one case had positive antimitochondrial antibodies and two others, positive antinuclear antibodies, for which they can be considered to belong to group II and group I, respectively; 21 cases remain. There are clinical, biochemical, and histologic elements and therapeutic response proper to a (AI-CAH); in this regard, it is suitable to mention here that in pediatric patients, and especially those whose ages range between breast-feeding infants and preschoolers, there is no well-defined pattern for immunological markers; on the other hand, histologic findings are characteristic and have been denominated cryptogenic hepatitis, with the peculiarity of responding to immunosuppressive therapy. Thus, this type of patients should be considered an autoimmune hepatitis carrier until the presentation of an immunological marker.

Eighteen children presented the hypergammaglobulinemia characteristic of this disease. It is known that pediatric patients could present the latter as well as the histologic findings of (AI-CAH).

Hematologic changes of anemia, leukopenia, and moderate thrombocytopenia have been observed in patients of this series. These patients have shown relapses, as described in the literature.

Regarding immunologic markers and evolution, it is known that type II is most frequent in children < 5 years of age and that it could possess an aggressive outset, even as a fulminated hepatitis, although this is not yet well-accepted.

It is very difficult in pediatrics to define which variables use immunologic markers, contrary to adults and especially in women in whom it is very likely to find such markers with great accuracy. On the other hand, histologic images can be misleading and mistaken as other illnesses that proceed with hepatopathy and should suitably be excluded: these diseases include, for example, Wilson disease, viral B and C hepatitis, alpha-1-antitrypsin deficiency, drug-induced hepatitis, and primary sclerosing cholangitis, which could be found by other laboratory studies and that have been considered in this study and by all our means within our reach.

Recently, other laboratory parameters have been referred in patients with chronic hepatopathies; these include serum quantification of leptins and antimitochondri-

al antibodies in saliva, which appear useful for identification of the chronic process more than for being specific for diagnosis of AI-CAH. Nonetheless, hepatopathies of the anti-cytosol hepatic type (anti-LCI type) and glutathione-S transferase M1 null genotype appear to be associated with the disease.^{7,15,18} Before establishing AI-CAH diagnosis, it would be convenient to clarify that serologic markers for hepatitis B and C should be negative, basically because these are infection types that tend to evolve into chronicity: this does not occur with hepatitis A, although this disease should be discarded because it is more related with fulminating forms, while bearing in mind that some cases of AI-CAH can adopt presentation of this serious clinical picture. In the series informing on positive testing for cytomegalovirus and mononucleosis, this cannot be considered an etiologic factor, in addition to the fact that there was no histologic liver imaging proper to these disorders.⁸⁻¹⁹

No patient reported on here had genetic studies performed on them. Recently, closely related alleles have been described; certainly within the following years, knowledge concerning this disease must be broadened.^{15,17,18}

The histologic pattern mentioned in previous paragraphs is the characteristic of AI-CAH, and recommendations for utilizing the Knodell scoring scale in chronic active hepatitis aids in valuation of post-treatment changes. Nonetheless, there has been questioning concerning the inclusion of fibrosis and cirrhosis because these diseases do not represent activity data but rather the effects of this activity or advanced disease stages.^{10,11} To evaluate disease evolution, it is necessary to carry out p.c. biopsies with intervals of 6 months to 1 year; biopsy intervals would depend upon the clinical behavior and the biochemical parameters: e.g., in a patient achieving remission in 2½ years, three to four biopsies would be necessary. In this series, average biopsy number was three, while in two cases seven to nine biopsies were required, respectively, for between 11 and 12 years of evolution. The Knodell scoring system was useful in nine cases to evaluate quantitatively treatment response to diminish points relative to liver damage; we will not go into this aspect further in this work, in that this comprises a theme for a specific review.

Hepatitis biopsy and histologic changes are important for diagnosis;²⁰ nevertheless, while the same imaging may be shared by hepatic diseases without immunology changes, such as Wilson's disease and alpha-1 antitrypsin, tissue obtained by means of p.c. biopsy should contain at least three to five portal spaces for adequate diagnosis.

From the 1950s, treatment for AI-CAH has consisted of immunosuppressor use; among these, the principal pharmaceutical and the drug that generally has obtained the best response is prednisone, especially in children > 5 years of age, with a less aggressive behavior; this is because in subjects of this age, prognosis is generally poor.

Initial dose is 2 mg x kg x day for 4–6 weeks for a maximum dosage of 60 mg/day, reducing dosage depending on transaminase diminution or normalization. This can occur rapidly, maintaining dosage between 10 and 15 mg daily, and even at lesser doses on alternate days for time lapses that can vary by 3 years or for indefinite periods. In some patients, treatment can be suspended for lapses during which patients are asymptomatic and have biochemical and histologic parameters of improvement or remission.

In this series of cases, 18 patients received prednisone as sole therapy: five abandoned treatment, 13 had a satisfactory response, and six presented clinical, biochemical, and histologic criteria for drug suspension.^{6,8,21} Of the nine patients who received prednisone, seven were administered treatment based on prednisone-azathioprine; there was biochemical improvement and favorable changes in their liver biopsies. With regard to this drug, azathioprine possesses fewer side effects; the recommended dose is 0.5–2 mg per kilo per day. Azathioprine associated with prednisone induces and maintains remission for prolonged periods and is indicated in patients with late response to prednisone or in those who present relapse. It is advantageous to maintain azathioprine at minimum doses of between 12 and 25 mg/day, taking care to watch for side effects (leukopenia, megablastosis, and interstitial pneumonia). Thus, this drug is recommended as a substitute for cyclosporin A, a good immunosuppressor drug whose drawbacks include its cost and its known undesirable side effects that include nephrotoxicity, hirsutism, and gingival hypertrophy.^{6,21-25}

Concerning use of cyclosporine and tacrolimus, it is necessary to obtain additional clinical experience for utilization, although during the past 5 years it has been recommended in cases without response to treatment and in cases demonstrating rapid evolution from fibrosis to cirrhosis, which occurs in approximately 25% of cases. Other pharmaceuticals such as rapamycin, mycophenolate mofetil, budesonide, ursodeoxycholic acid, cyclophosphamide, deflazacort, and 6-mercaptopurine require additional clinical assays. In case of therapeutic failure with these alternatives, patients should be referred for liver transplant; nonetheless, this procedure does not appear to be the definitive solution because AI-CAH recurrence has been described in children receiving liver transplant. On the other hand, a percentage of patients with another type of hepatopathy in whom transplant was carried out developed AI-CAH as a complication at a later date.^{19,21-28}

According to what has been previously mentioned in this work, the most effective therapy in use at present continues to be prednisone, and in specific cases in association with azathioprine. In this series, it can be observed that use of this double scheme was required in seven children.

On the other hand, it is suitable to bear AI-CAH in mind, notwithstanding its low frequency of presentation, in that it comprises 3% of chronic liver diseases and in some countries has been estimated as 4 x 100,000 in general pop-

ulation.^{23,24} This disease should be considered especially among patients with a history of hepatic disease with insidious course, and also in those who are asymptomatic and have elevated transaminases and in children presenting hepatomegalia or hepatosplenomegalia. Additionally, on taking into account that we do not know to date the origin of the disease it is recommendable to ascertain the child's clinical history, the patient's antecedent of having repeatedly received liver disorder-associated drugs such as acetaminophen, phenobarbital, nitrofurantoin, isoniazid, oxyphen-satin, and alpha-methyl dopa; while it is certain that the cause of AI-CAH has not been demonstrated it is nonetheless desirable to exercise caution with these previously mentioned drugs and to avoid their use, especially in individuals demonstrating in transaminases elevation, even at levels discretely higher than normal.^{6,8,25-33}

Because this is a disease whose nature is unknown, which manifests a mortality of 50% prior to the age of 3 years in untreated children, and which even in patients identified in a timely fashion a mortality of 21–30% exists, in this report mortality was 15%. Three children were < 5 years of age; of these three children, two merit special mention: notwithstanding the age at which they were studied (2 and 6 months), they demonstrated histologic imaging of chronic active hepatitis. One was positive on one occasion for cytomegalovirus, with the inability to sustain this as an etiologic factor; on the other hand, both patients had antimitochondrial antibodies taken and that were negative; thus, it is difficult to imagine the possibility that if it had been primary biliary cirrhosis, their chronic hepatitis course was aggressive with fulminating evolution, fibrosis, cirrhosis, and liver insufficiency. The remaining patient, who was 2 months of age and who did not receive drugs, went to two out-patient consultations-at 6 months and at 1 year of age-and subsequently abandoned assisting at hospital control appointments. One female patient who is at present 19 years of age developed type I diabetes mellitus, probably a consequence of the same AI-CAH-related immunologic process described in the literature.²⁻⁶ With respect to 5-year survival in the present series, this was 56.5% in cases with long-term follow-up.

The treating physician is obliged to clearly inform the relatives and the patient him/herself, when possible, concerning everything concerning the disease, utilizing easily understood concepts and above all explaining the need for not abandoning treatment, even when this treatment possesses the risk of side effects and when the treatment should be administered over the long term, to date the surest method for maintaining prolonged AI-CAH remissions and providing a better quality of life.^{11,26,27}

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