Autoimmune hepatitis in the pediatric age

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Abstract

In pediatrics, autoimmune hepatitis and sclerosing cholangitis are immune-mediated diseases that affect the liver. Autoimmune hepatitis is a disease of unknown etiology characterized by interface hepatitis, hypergammaglobulinemia, circulating autoantibodies and a favorable response to immunosuppression. It is an eminently pediatric disease with a high prevalence in young women. Therapy should be instituted promptly to prevent rapid deterioration, promote remission of disease and long-term survival. The persistent lack of response or lack of adherence to treatment results in end-stage liver disease; these patients, and those with fulminant hepatic failure at the time of diagnosis, will require liver transplantation.

Key words: Autoimmune hepatitis. Chronic liver disease. Seronegative hepatitis.

Hepatitis autoinmune en la edad pediátrica

Resumen

En pediatría, la hepatitis autoinmune y la colangitis esclerosante son patologías de afección hepática cuyo mecanismo de daño es inmunológico. La hepatitis autoinmune es una enfermedad de etiología desconocida, caracterizada por hepatitis de interfase, hipergammaglobulinemia, autoanticuerpos circulantes y una respuesta favorable a la inmunosupresión. Es una enfermedad eminentemente pediátrica, con una afección prevalente hacia mujeres jóvenes. La terapia debe ser instituida con prontitud para prevenir el deterioro rápido, promover la remisión de la enfermedad y la supervivencia a largo plazo. La falta persistente de respuesta o la falta de adherencia al tratamiento dan como resultado una enfermedad hepática terminal. Estos pacientes, y aquellos con insuficiencia hepática fulminante en el momento del diagnóstico, requerirán trasplante hepático.

Palabras clave: Hepatitis autoinmune. Hepatopatía crónica. Hepatitis seronegativa.

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Introduction

Autoimmune hepatitis (AH) is an inflammatory liver disease characterized by hypertransaminasemia, polyclonal hypergammaglobulinemia, high serum titers of non-organ-specific and liver-specific autoantibodies, in the absence of another liver disease and marked by an interface hepatitis^{1,2}.

Classification

AH is classified into two subtypes according to the type of serum antibodies detected at diagnosis (Table 1)^{3,4}.

- a) Type 1 autoimmune hepatitis (T1AH): it is characterized by the presence of antinuclear antibodies (ANAs) and anti-smooth-muscle antibodies (SMA), which can be detected alone or with other antibodies.
- b) Type 2 autoimmune hepatitis (T2AH): it is characterized by the presence of liver and kidney anti-mitochondrial autoantibodies (LKM1) or anti-liver cytosol type 1 antibodies (anti-LC-1)
- c) Type 3 autoimmune hepatitis (T3AH) has also been proposed and is characterized by the presence of antibodies to a soluble liver antigen (SLA), also denominated liver/pancreatic antigen (L/P). It has been described alone or associated with other autoantibodies, mainly SMA, so some authors considered it to be a variant of T1AH⁵.

Recently, seronegative autoimmune hepatitis has been described, which should be suspected in children with clinical or biochemical data of chronic liver disease of unknown cause with compatible histopathology. In this case, immunosuppressive treatment must be started rapidly despite a lack of serologic markers and even in children with normal or low levels of serum gamma-globulins⁶.

Epidemiology

The disease can be found in every geographic region of the world; its prevalence in children is unknown. As in other autoimmune diseases, the greatest incidence occurs during the prepubertal age, although it can be diagnosed at any age. Forty-percent of patients with T1AH and 80% of those with T2AH are diagnosed during childhood⁷. Over the last years, an increasing incidence of the disease in children and adolescents has been reported⁸.

In Mexican children, the observed average age at diagnosis is ten years for T1AH and six years for T2AH, with a predominance in females with a ratio of 3:1⁹.

Etiopathogenesis

The etiology behind AH is still unknown; it is a complex disease, in which environmental factors and the host's genetic susceptibility lead to a loss of self-tolerance and, later, to the development of the disease¹⁰.

Genetic factors

Genetic susceptibility is partially determined by the presence of specific molecules of class II major histocompatibility complex (MCH II), and more directly, to the human leukocyte antigen (HLA)¹¹. The main associations are with HLA-DR3 and HLA-DR4 (DRB1 * 03 and DRB1 * 04) in Europeans and Americans. In Japan, Argentina and Mexico, susceptibility is related to DRB1 * 0405 and DRB1 * 0404. In children, HLA-DRB1 * 1301 is associated with increased AH susceptibility and determines prognosis and treatment response (Table 2)¹²⁻¹⁸.

Immune factors

The pathophysiological mechanism consists of an inflammatory response by T lymphocytes, mainly T helper cells, B lymphocytes, macrophages and NK cells. The triggering factor or the factors that promote this inflammatory response are still unknown¹⁹.

Some studies have demonstrated that patients with AH have decreased numbers and impaired function of CD4+ CD25+ T lymphocytes, which are known as T regulatory cells. These cells suppress proliferation and the responses to cytokines of CD4+ and CD8+ effector lymphocytes and decrease regulation of the functions of macrophages, dendritic cells, NK cells and B lymphocytes²⁰⁻²².

Surface markers involved in the anti-inflammatory mechanisms include cytotoxic T lymphocyte antigen-4 (CTLA-4), FOXP3 transcription regulator factor and the cellular adhesion molecular CD62L^{22,23}. In patients with AH, NK cells are reduced, producing lower levels of interleukin 4 (IL-4) and IL-2, which results in a reduction of the surface expression of CTLA-4 in CD4+ T cells, playing a fundamental role in autoimmune liver damage²⁴. Another possibility implicates the presence of autoreactive CD4+ and CD8+ T cells that could damage liver cells. These cells are present in healthy people but increased by ten times in patients with AH²⁵.

Increased expression of the Fas membrane protein has been found in the surface of lymphocytes of patients with AH; this could be a key mechanism leading to autoimmunity. Fas (CD95) is part of the tumor

Table 1. Differences between two subtypes of autoimmune hepatitis in children⁴

	Type 1 AH	Type 2 AH
Predominant age	Adolescence	Schoolchildren and preschoolers
Typical onset	Chronic and insidious	Acute hepatitis
Cirrhosis at diagnosis	Frequent	Less frequent
Hypergammaglobulinemia	++++	+ / ++
Biliary lesions	Possible	Absent
Extrahepatic manifestations	Arthritis Autoimmune purpura	Graves' disease Autoimmune thyroiditis Vitiligo Alopecia
Typical antibodies	ANA SMA	LKM-1
Other antibodies	SLA/LP p-ANCA ASGP-r	LC-1

*AH, autoimmune hepatitis; ANA, antinuclear antibodies; SMA, anti-smooth muscle antibodies; SLA/LP, antibodies to a soluble liver antigen/liver/pancreatic antigen; p-ANCA, peri-nuclear antineutrophil cytoplasmic antibodies; ASGP-r, asialoglycoprotein receptor antibody; LKM-1, liver and kidney anti-microsomal autoantibodies; LC-1, anti-liver cytosol type 1 antibodies

Table 2. Association of HLA and autoimmune hepatitis in children

Reference	Total number of patients/controls (number of children)	Assessed HLA	Conclusions
Fortes et al. ¹⁵	41/111 (13)	HLA-A, -B, -C, -DR and DQ	No significant differences regarding HLA-A and -C were found between groups. For HLA class I, an increase in the frequency of B * 08, B * 18, B * 45 and B * 50 was observed. HLA B * 40 was more frequent in healthy controls; For HLA class II, an increase in the frequency of HLA-DQB1 * 02, -DQB1 * 04, HLA-DRB1 * 03, DRB1 * 13 and DRB3 was observed. HLA-DRB1 * 1301 and -DRB1 * 0301 were the most frequent in children
Fainboim et al. ¹⁶	52/197	HLA-A, -B, -C, -DR and -DQ	No significant associations with HLA class I antigens was found. The HLA-DR6 group (HLA-DRB1) was the most frequent, mainly HLA-DRB1 * 1301. HLA-DQ analysis showed an association with HLA-DQB1 * 0603
Pando et al. ¹⁷	206/208 (122)	HLA-DR and -DQ	The frequencies of HLA-DRB1 * 1301, -DRB1 * 0301, -DQA1 * 0103, -DQB1 * 0603 increased significantly in patients with AH. HLA-DRB1 * 1301 was associated with earlier age at disease onset; this allele is associated with AH in children. HLA-DRB1 * 1302 works as a protection factor
Bittencourt et al. ¹⁸	139/129 (74)	HLA-DRB and -DQB1	In patients with type 1 AH, there was a significant increase in the HLA-DRB1 * 13, -DRB1 * 03, -DRB3 and -DQB1 * 06 alleles. HLA-DRB1 * 13 was more frequent in children than in adults. The low frequency of HLA-DQB1 * 0301 can indicate a protective role of this allele; In type 2 AH, a significant increase in DRB1 * 07, DRB1 * 03, DRB4 y DQB1 * 02 was observed

HLA, human leukocyte antigen; AH, autoimmune hepatitis

necrosis factor family and induces apoptosis through binding of its ligand (FasL/CD95L)²⁶.

Environmental factors

Among the drugs associated with AH are nitrofurantoin, minocycline, methyldopa, diclofenac, atorvastatin, propylthiouracil, isoniazid, anti-retroviral agents used for the human immunodeficiency virus and anti-tumor necrosis factor alpha (TNF- α). Several herbal products have been proposed as predisposing agents. The exact cause of drug-induced AH is unknown but can be attributed to the hepatotoxic effect of these chemical compounds. Hepatitis A, B or C virus, in addition to measles, cytomegalovirus and Epstein Barr virus have been implicated as triggers²⁷⁻³⁰.

Clinical course

The clinical course of AH is characterized by an ample range of symptoms, which oscillate between mild to severe, with or without extra-hepatic manifestations. In approximately half of the patients, onset is similar to viral hepatitis; manifestations such as asthenia, nausea, vomit, anorexia, abdominal pain followed by jaundice can exist, even as a fulminant form of acute liver failure. It can present insidiously, with unspecific symptoms such as relapsing jaundice, headache, anorexia, weight loss and delay in the onset of menarche or amenorrhea, with signs of hypercortisolism, which last several months and even years before the diagnosis. Some patients do not have a history of jaundice, and the diagnosis is carried out due to complications of portal hypertension, such as splenomegaly or variceal gastrointestinal bleeding. Physical examination reflects the duration and severity of the disease; 25% of patients have a normal physical examination, although hepatomegaly is the most common finding. Cirrhosis is usually accompanied by splenomegaly and liver disease^{7,9,31-34}.

Associated autoimmune diseases

Forty-percent of patients with AH has an associated autoimmune disease³⁵. The most frequent are: autoimmune thyroiditis, systemic lupus erythematosus, vitiligo, inflammatory bowel disease, celiac disease, type 1 diabetes mellitus, mixed connective tissue disease, arthritis, Sjögren syndrome, primary thrombocytopenic purpura, hemolytic anemia, multiple sclerosis, autoimmune polyglandular³⁵⁻⁴¹. Family and personal history must be inquired in detail.

Diagnosis

A high index of suspicion for the disease is required since there are no specific symptoms or complementary physical signs that are pathognomonic of the disease. However, typical parameters in combination with the exclusion of other entities can help to establish the diagnosis.

Diagnostic criteria

The first criteria were published in 1993 by the International Autoimmune Hepatitis Group. In 2008, the same group proposed the simplified criteria (Table 3)⁴², which have been validated and proven to have adequate sensibility and specificity for the early recognition of the disease and the timely start of immunosuppressive treatment⁴³⁻⁴⁵.

Laboratory data

Classically, hypertransaminasemia and hypergammaglobulinemia are found. These findings are not only useful for diagnosis but are also important as prognostic indicators. Regularly, the pattern of affection corresponds to cytolysis, but cholestasis with elevated direct bilirubin, gamma-glutamyl transferase, and alkaline phosphatase can be present. Occasionally, a deficit of IgA and a decrease C3 and C4 complement proteins can be observed^{2,27}.

Autoantibodies

Its detection constitutes an important diagnostic tool that allows classification in the various types of AH (Table 4)^{28,47-51}.

Histopathological findings

Liver biopsy is necessary for the diagnosis of AH, to determine the level of fibrosis and inflammatory activity, as well as to corroborate remission and absence of activity before suspending the immunosuppressive treatment. It is important to highlight that aminotransferase and IgG values do not reflect the level of tissue damage⁵².

The typical lesion consists of an inflammatory infiltrate of mononuclear and plasmatic cells that surpass the limiting plate between the portal space and the liver lobule (interface hepatitis). This lesion can extend to form necrotic bridges with inflammatory activity between different portal spaces, which are later replaced by fibrous

Table 3. Simplified diagnostic criteria⁴²

Parameter	Results	Score
ANA or SMA	Greater than or equal 1:40	1
ANA or SMA	Greater than or equal 1:80	2
Anti LKM-1	Greater than or equal 1:40	2
Anti SLA/LP	Positive	2
Immunoglobulin G	Above the normal upper limit	1
	>1.10 the normal value	2
Liver histology	Compatible with AH	1
	Typical AH (Interface hepatitis)	2
Viral hepatitis	Absent	2
	Present	0
		≥7: definitive AH
		≥6: probable AH

ANA, antinuclear antibodies; SMA, anti-smooth muscle antibodies; LKM-1, liver and kidney anti-microsomal autoantibodies; SLA/LP, antibodies to a soluble liver antigen/liver/pancreatic antigen; AH, autoimmune hepatitis

Table 4. Autoantibodies in autoimmune hepatitis

Antibody	Clinical significance
Antinuclear (ANA)	Type 1 AH diagnosis In most patients the pattern is homogeneous, but it can be granular or fine speckled Associated with the DRB1 * 0401 allele
Anti-Smooth muscle (SMA)	More specific diagnostic marker of type 1 AH
Liver and kidney anti-microsomal autoantibodies (LKM-1)	Highly specific for type 2 AH 2 Directed against the P450 cytochrome
Soluble liver antigen (SLA)	High specificity, may be absent when other markers are absent Prediction of relapses and treatment dependence Associated with the DRB1 * 0301 allele Greater incidence of death due to liver failure
Anti-liver cytosol type 1 antibodies (LC-1)	Present when other markers such as ANA, SMA, LKM1 are absent Directed against the formiminotransferase cyclodeaminase Early age onset and other autoimmune diseases Marked liver inflammation and rapid progression to cirrhosis.
Anti-actin	Treatment dependence and progression to liver failure Severe clinical and histological disease
Perinuclear antineutrophil cytoplasmic antibodies (p-ANCA)	Observed in type 1 AH, may help the diagnosis when other tests are negative
Asialoglycoprotein receptor antibody (ASGP-r)	Directed against the transmembrane surface of the hepatocyte Associated with histological activity When persistent, it is associated with relapses after steroid withdrawal
Anti-chromatin	Associated with ANAs Relapse predictor after withdrawal of immunosuppressive treatment It presents with higher levels of IgG
Anti-citrullinated peptide	It has been described in 9-11% of patients with AH without arthritis Associated with greater liver damage and cirrhosis
Anti-DNA	Failure to treatment with steroids. Associated with the HLA DR4 haplotype.
Anti-LKM3	It has been described in 7% of patients with AH associated with Hepatitis C Virus.

AH, autoimmune hepatitis; HLA, human leukocyte antigen

tracts. The inflammatory infiltrate can also be present predominantly in the liver sinusoids (lobular hepatitis), and as liver regeneration with rosette formation^{53,54}.

Differential diagnosis

The differential diagnosis of AH in children and adolescents is quite extensive and requires a meticulous approach. Chronic viral hepatitis, mainly B and C, can present with a similar clinical course; Wilson's disease should be excluded. Sclerosing cholangitis should be ruled out, and since these patients can represent a considerable proportion of children with autoimmune liver disease, a cholangiography should be performed when suspicion of AH arises. Liver disease associated with alpha 1 anti-trypsin can resemble AH in children. Children with non-alcoholic fatty liver disease can have low antibody titers; clinical differentiation is simple, although occasionally a liver biopsy to distinguish these two entities is required^{1,55-57}.

Treatment

The cornerstone of treatment in AH is immunosuppressive therapy with corticosteroids. Around 80% of the cases have a positive response to this therapy. The treatment scheme consists of prednisone at a dose of 2 mg/kg/day (maximum of 60 mg/day), which is progressively decreased based on the biochemical response within 4 to 8 weeks, up to a maintenance dose of 2.5-5 mg. The goal is to achieve an 80% reduction in the levels of transaminases in the first eight weeks, while a complete normalization can be obtained in the following months. After 6-9 months of therapy, up to 75-90% of patients show normal values in their liver function tests. In the first phase of treatment, strict surveillance with weekly assessments of liver function tests is recommended to adjust treatment accordingly^{58,59}.

Azathioprine can be added to the treatment as a steroid-sparing agent. Combined treatment of prednisone and azathioprine decreases the frequency of steroid-induced secondary adverse events. The initial dose of 0.5 mg/kg/day can be increased gradually up to 2 mg/kg/day in the absence of signs of toxicity to achieve and maintain control of the disease. Given the minimal side effect of low-dose corticosteroids even with long-term use, combined therapy is suggested to maintain disease remission. A maintenance dose of 1-1.5 mg/kg/day of azathioprine, with a low dose of corticosteroids, seems to be an effective and safe long-term treatment scheme^{59,60}.

Response to treatment and follow-up

The goal of treatment is to control the disease to prevent the development of cirrhosis and its complications.

Remission is considered when the levels of transaminases and immunoglobulin G (IgG) are normal and autoantibodies are negative or in low titers. Resolution of histological damage is slower than serological normalization, and biochemical remission may not reflect histological resolution. Relapses are characterized by an increase in the levels of transaminases, IgG positivity and high titers of autoantibodies; it occurs in 40% of patients and requires treatment with high-dose steroids⁶¹.

There are no clear indications regarding the duration of the immunosuppressive therapy, but after three years of biochemical remission and in the presence of histological resolution of the disease, gradual discontinuation of therapy is feasible if close serological monitoring is continued. Avoiding attempts to suspend treatment during the prepubertal period and the first three years from the diagnosis is advisable due to the reported high frequency of relapses in these phases⁶².

Follow-up biopsies are recommended before the suspension of immunosuppressive treatment or in patients with incomplete remission on standard therapy to exclude an alternative diagnosis or pharmacological toxicity and to evaluate the hepatitis activity index to stratify the disease and decide whether treatment escalation is necessary⁶³.

In patients receiving long-term corticosteroid treatment, evaluation of mineral bone density at the beginning of treatment and annually is recommended. Complementary therapies, such as regular exercise and vitamin D and calcium supplementation are also recommended⁵⁸.

Difficult-to-treat AH

In approximately 10% of patients, standard immunosuppression cannot induce or maintain disease remission, or it is not well tolerated long-term due to its secondary effects. If the patient does not respond to first-line treatment, other therapies should be considered. Ensuring adequate patient adherence is vital, particularly for adolescents, which have a lower probability of agreeing with their treatment⁶⁴. The presence of cirrhosis at the onset of treatment increases the risk of treatment failure⁵³.

Budesonide is a synthetic steroid with a high first-pass metabolism in the liver, with minimal secondary effects compared to conventional steroids, and acts

as anti-inflammatory and immunosuppressive agent⁶⁵. Oral budesonide and azathioprine can induce and maintain remission in pediatric patients with AH and can be considered as an alternative to prednisone. This treatment causes less adverse effects; nevertheless, it can be less effective than prednisone for induction of remission⁶⁶. It should not be used in patients with cirrhosis in which portal hypertension will reduce the first-pass metabolism; it also has the disadvantage of being administered every 8 hours compared to prednisolone, which may be administered once a day⁶⁷.

Mycophenolate is a non-competitive inhibitor of the inosine monophosphate dehydrogenase, which blocks *de novo* synthesis of purines. Mycophenolate has a selective action on lymphocyte activation, with a marked reduction of T and B lymphocyte proliferation. It has been proposed as a useful second-line therapy in children and adolescents with AH that does not respond to conventional treatment with steroids and azathioprine⁶⁸. Although mycophenolate seems to be a promising agent that is especially useful as rescue therapy in difficult patients, a significant disadvantage is its high cost⁶⁹.

Cyclosporine inhibits cellular activation of T cells; it has been studied in children and shows promising results, and it can be considered as an alternative therapy to steroids in patients not achieving complete remission. The main limitation of cyclosporine is its potential side effects, such as nephrotoxicity, hypertension and malignancy risk. Therefore, multicentric trials including a large number of children treated for a long time are needed to identify the clear indication and the safety profile of cyclosporine in children^{70,71}.

Tacrolimus leads to inhibition of the synthesis of cytokines (IL-2, IL-3 and interferon-alpha [INF- α]), expression of the IL-2 receptor and generation of cytotoxic T cells. There is limited evidence of its use as a treatment of AH in children, but some reports show that it can be useful when associated with steroids in cases of refractoriness to standard treatment. Special attention is required with regular monitoring of tacrolimus levels to prevent side effects caused by high blood concentrations, such as seizures and nephrotoxicity⁷²⁻⁷⁴.

Rituximab is a chimeric anti CD-20 monoclonal antibody, a surface marker expressed in B cells initially developed for the treatment of B cell lymphoma. Rituximab has shown to be effective for the treatment of autoimmune diseases, which suggests that it could also be effective in patients with AH, experience in AH is limited, so controlled clinical trials are needed before

rituximab can be recommended as an alternative treatment for AH⁷⁵⁻⁷⁷.

Infliximab, etanercept, and adalimumab are anti-TNF α agents commonly used for the treatment of immune-mediated diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease⁷⁸. There is emerging evidence that anti-TNF antibodies are capable of inducing remission in patients with AH in whom standard or alternative therapeutic options have been exhausted; nevertheless, precipitation of AH has also been observed during treatment with anti-TNK antibodies⁷⁹⁻⁸¹. Future studies would have to define the role of anti-TNK antibodies in difficult-to-treat cases of AH.

Ursodeoxycholic acid is a hydrophilic bile acid with immunomodulatory capacities through reduction of liver expression of HLA-A1 and suppresses production of immunoglobulin and cytokines^{82,83}. Based on the relatively benign side effects profile of ursodeoxycholic acid, its use may be considered in patients with lower disease activity as an attempt to induce remission; nevertheless, experience in children is limited. In patients with more active AH, the ursodeoxycholic acid may allow a reduction in the dose of immunosuppressors, particularly steroids⁸⁴.

Liver transplantation

AH represents 2-3% of the indications for liver transplant in pediatric patients⁵⁸. In general, cases of AH that require liver transplantation are patients with fulminant hepatitis that do not respond to standard pharmacologic treatment and, in rare occasions, patients with progressive liver disease despite adequate immunosuppressor treatment. The risk of recurrence in AH after liver transplantation seems to be greater in patients that have been transplanted during the active phase of the disease; nevertheless, recurrence of AH can also occur many years later⁸⁵⁻⁸⁷. Long-term steroid therapy is recommended in patients that have had a liver transplant due to AH⁸⁸. Post-transplant survival in AH is good, with 5-year survival rates of up to 90-95%⁸⁹.

Prognosis

AH is an important cause of liver disease in children, having a particularly aggressive course in young patients. Those patients that have a good response to treatment have a good prognosis. Thus, adequate adherence to immunosuppressive therapy should be

ensured. Parents and adolescents should have sufficient knowledge about the disease and its chronic character, since probably patients will need prolonged or lifelong treatments, as well as suspension and failure to comply with treatment properly, carries a high risk of relapse^{90,91}.

Given that it has a variable presentation, AH should be suspected in every case of liver disease in which common etiologies are excluded so appropriate treatment can be rapidly started.

Future therapies for AH will use molecular intervention directed to the mechanisms of autoimmune damage. New treatment modalities are under investigation, one of the current treatment goals is to restore the function of autologous T-regulatory cells and use them as a form of immunotherapy^{92,93}. Another option for specific intervention is the use of molecules that completely inhibit autoantigen binding to presenting cells, reducing antigen presentation and, consequently, lymphocyte activation, based on the use of monoclonal antibodies against the cytokines implicated in the genesis of liver disease⁹⁴.

Conclusions

AH is an eminently pediatric disease, with an incidence increase in recent years, so it must be suspected especially patients of school age and adolescents with hepatomegaly and jaundice. The presentation can be insidious, so this disease should be part of the differential diagnosis when evaluating unspecific symptoms such as headaches, anorexia, weight loss, among others. Timely referral to specialized centers should be done in patients suspected of having AH, even if asymptomatic, but with compatible biochemical signs, mainly hypertransaminasemia and hypergammaglobulinemia. Early treatment will avoid disease progression, the development of complications and improve patient survival.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflicts of interest

The authors declare no conflicts of interest.

References

- Roberts EA. Autoimmune hepatitis from the paediatric perspective. *Liver Int.* 2011;31:1424-31.
- Zachou K, Muratori P, Koukoulis GK, Granito A, Gatselis N, Fabbri A, et al. Review article: autoimmune hepatitis - current management and challenges. *Aliment Pharmacol Ther.* 2013;38:887-913.
- Maggiore G, Nastasio S, Sciveres M. Juvenile autoimmune hepatitis: Spectrum of the disease. *World J Hepatol.* 2014;6:464-76.
- Maggiore G, Sciveres M. Autoimmune hepatitis: A childhood disease. *Curr Pediatr Rev.* 2005;1:73-90.
- Vitozzi S, Djilali-Saiah I, Lapiere P, Alvarez F. Anti-soluble liver antigen/liver-pancreas (SLA/LP) antibodies in pediatric patients with autoimmune hepatitis. *Autoimmunity.* 2002;35:485-92.
- Oettinger R, Brunnberg A, Gerner P, Wintermeyer P, Jenke A, Wirth S. Clinical features and biochemical data of Caucasian children at diagnosis of autoimmune hepatitis. *J Autoimmun.* 2005;24:79-84.
- Maggiore G, Socie G, Sciveres M, Roque-Afonso AM, Nastasio S, Johanet C, et al. Seronegative autoimmune hepatitis in children: Spectrum of disorders. *Dig Liver Dis.* 2016;48:785-91.
- Mieli-Vergani G, Vergani D. Autoimmune hepatitis in children: what is different from adult AIH? *Semin Liver Dis.* 2009;29:297-306.
- Nares-Cisneros J, Jaramillo-Rodríguez Y. Hepatitis autoimmune en niños: evolución de 20 casos del norte de México. *Rev Gastroenterol Mex.* 2014;79:238-43.
- Franque S, Vonghia L, Ramon A, Michielsen P. Epidemiology and treatment of autoimmune hepatitis. *Hepat Med.* 2012;4:1-10.
- Tang J, Zhou C, Zhang ZJ, Zheng SS. Association of polymorphisms in non-classic MHC genes with susceptibility to autoimmune hepatitis. *Hepatobiliary Pancreat Dis Int.* 2012;11:125-31.
- Donaldson PT, Doherty DG, Hayllar KM, McFarlane IG, Johnson PJ, Williams R. Susceptibility to autoimmune chronic active hepatitis: human leukocyte antigens DR4 and A1-B8-DR3 are independent risk factors. *Hepatology.* 1991;13:701-6.
- Czaja AJ, Donaldson PT. Genetic susceptibilities for immune expression and liver cell injury in autoimmune hepatitis. *Immunol Rev.* 2000;174:250-9.
- Czaja AJ, Souto EO, Bittencourt PL, Cançado EL, Porta G, Goldberg AC, et al. Clinical distinctions and pathogenic implications of type 1 autoimmune hepatitis in Brazil and the United States. *J Hepatol.* 2002;37:302-8.
- Fortes M del P, Machado IV, Gil G, Fernández-Mestre M, Dagher L, León RV, et al. Genetic contribution of major histocompatibility complex class II region to type 1 autoimmune hepatitis susceptibility in Venezuela. *Liver Int.* 2007;27:1409-16.
- Fainboim L, Marcos Y, Pando M, Capucchio M, Reyes GB, Galoppo C, et al. Chronic active autoimmune hepatitis in children. Strong association with a particular HLA-DR6 (DRB1*1301) haplotype. *Hum Immunol.* 1994;41:146-50.
- Pando M, Larriba J, Fernandez GC, Fainboim H, Ciocca M, Ramonet M, et al. Pediatric and adult forms of type I autoimmune hepatitis in Argentina: evidence for differential genetic predisposition. *Hepatology.* 1999;30:1374-80.
- Bittencourt PL, Goldberg AC, Cançado EL, Porta G, Carrilho FJ, Farias AQ, et al. Genetic heterogeneity in susceptibility to autoimmune hepatitis types 1 and 2. *Am J Gastroenterol.* 1999;94:1906-13.
- Lapiere P, Béland K, Alvarez F. Pathogenesis of autoimmune hepatitis: from break of tolerance to immune-mediated hepatocyte apoptosis. *Transl Res.* 2007;149:107-13.
- Longhi MS, Hussain MJ, Mitry RR, Arora SK, Mieli-Vergani G, Vergani D, et al. Functional study of CD4+CD25+ regulatory T cells in health and autoimmune hepatitis. *J Immunol.* 2006;176:4484-91.
- Ferri S, Longhi MS, De Molo C, Lalané C, Muratori P, Granito A, et al. A multifaceted imbalance of T cells with regulatory function characterizes type 1 autoimmune hepatitis. *Hepatology.* 2010;52:999-1007.
- Ferri Liu PM, de Miranda DM, Fagundes EDT, Ferreira AR, Simões e Silva AC. Autoimmune hepatitis in childhood: The role of genetic and immune factors. *World J Gastroenterol.* 2013;19:4455-63.
- Longhi MS, Meda F, Wang P, Samyn M, Mieli-Vergani G, Vergani D, et al. Expansion and de novo generation of potentially therapeutic regulatory T cells in patients with autoimmune hepatitis. *Hepatology.* 2008;47:581-91.

24. La Cava A, Van Kaer L. CD4+CD25+ Tregs and NKT cells: regulators regulating regulators. *Trends Immunol.* 2006;27:322-7.
25. Ajuenor MN, Hogaboam CM, Le T, Proudfoot AE, Swain MG. CCL3/ MIP-1 α is pro-inflammatory in murine T cell-mediated hepatitis by recruiting CCR1-expressing CD4(+) T cells to the liver. *Eur J Immunol.* 2004;34:2907-18.
26. Ogawa S, Sakaguchi K, Takaki A, Shiraga K, Sawayama T, Mouri H, et al. Increase in CD95 (Fas/APO-1)-positive CD4+ and CD8+ T cells in peripheral blood derived from patients with autoimmune hepatitis or chronic hepatitis C with autoimmune phenomena. *J Gastroenterol Hepatol.* 2000;15:69-75.
27. Gatselis NK, Zachou K, Koukoulis GK, Dalekos GN. Autoimmune hepatitis, one disease with many faces: Etiopathogenetic, clinico-laboratory and histological characteristics. *World J Gastroenterol.* 2015; 21: 60-83.
28. Makol A, Watt KD, Chowdhary VR. Autoimmune hepatitis: A review of current diagnosis and treatment. *Hepat Res Treat.* 2011;2011:390916.
29. Elfaramawy AA, Elhossiny RM, Abbas AA, Aziz HM. HLA-DRB1 as a risk factor in children with autoimmune hepatitis and its relation to hepatitis A infection. *Ital J Pediatr.* 2010;36:73.
30. Higuera-de la Tijera M, Servín-Caamaño AI, Alexanderson-Rosas EG. Toxicidad hepática inducida por fármacos y herbolaria. *Rev Med Hosp Gen Mex.* 2012;75:230-7.
31. Gregorio GV, Portmann B, Reid F, Donaldson PT, Doherty DG, McCartney M, et al. Autoimmune hepatitis in childhood: a 20-year experience. *Hepatology.* 1997;25:541-7.
32. Minemura M, Tajiri K, Shimizu Y. Systemic abnormalities in liver disease. *World J Gastroenterol.* 2009;15: 2960-74.
33. Floreani A, Liberal R, Vergani D, Mieli-Vergani G. Autoimmune hepatitis: Contrasts and comparisons in children and adults - a comprehensive review. *J Autoimmun.* 2013;46:7-16.
34. Dehghani SM, Haghighat M, Imanieh MH, Honar N, Negarestani AM, Malekpour A, et al. Autoimmune hepatitis in children: experiences in a tertiary center. *Iran J Pediatr.* 2013; 23:302-8.
35. Teufel A, Weinmann A, Kahaly GJ, Centner C, Piendl A, Wörms M, et al. Concurrent autoimmune diseases in patients with autoimmune hepatitis. *J Clin Gastroenterol.* 2010;44:208-13.
36. Beisel C, Weiler-Normann C, Teufel A, Lohse AW. Association of autoimmune hepatitis and systemic lupus erythematosus: A case series and review of the literature. *World J Gastroenterol.* 2014; 20:12662-7.
37. Sedej K, Toplak N, Praprotnik M, Luzar B, Breclj J, Avčinet T. Autoimmune hepatitis as a presenting manifestation of mixed connective tissue disease in a child Case report and review of the literature. *Pediatr Rheumatol.* 2015;13:47.
38. Al-Hussaini AA, Alzahrani MD, Alenizi AS, Suliman NM, Khan MA, Alharbi SA, et al. Autoimmune hepatitis related autoantibodies in children with type 1 diabetes. *Diabetol Metab Syndr.* 2014;6:38.
39. DeFilippis EM, Kumar S. Clinical presentation and outcomes of autoimmune hepatitis in inflammatory bowel disease. *Dig Dis Sci.* 2015;60: 2873-80.
40. Najafi M, Sadjadei N, Eftekhari K, Khodadad A, Motamed F, Fallahi GH, et al. Prevalence of celiac disease in children with autoimmune hepatitis and vice versa. *Iran J Pediatr.* 2014;24:723-8.
41. Ito A, Yoshizawa K, Fujimori K, Morita S, Shigeno T, Maejima T. Autoimmune hepatitis associated with immune thrombocytopenic purpura. *Intern Med.* 2017;56:143-7.
42. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology.* 2008;48:169-76.
43. Mileti E, Rosenthal P, Peters MG. Validation and modification of simplified diagnostic criteria for autoimmune hepatitis in children. *Clin Gastroenterol Hepatol.* 2012;10:417-21.
44. Ferri PM, Ferreira AR, Miranda DM, Simões E Silva AC. Diagnostic criteria for autoimmune hepatitis in children: a challenge for pediatric hepatologists. *World J Gastroenterol.* 2012;18:4470-3.
45. Abdollahi MR, Somi MH, Faraji E. Role of international criteria in the diagnosis of autoimmune hepatitis. *World J Gastroenterol.* 2013;19: 3629-33.
46. Zachou K, Oikonomou K, Renaudineau Y, Chauveau A, Gatselis N, Youinou P, et al. Anti- α actinin antibodies as new predictors of response to treatment in autoimmune hepatitis type 1. *Aliment Pharmacol Ther.* 2012;35:116-25.
47. Ma Y, Okamoto M, Thomas MG, Bogdanos DP, Lopes AR, Portmann B, et al. Antibodies to conformational epitopes of soluble liver antigen define a severe form of autoimmune liver disease. *Hepatology.* 2002;35: 658-64.
48. Bridoux-Henno L, Maggiore G, Johanet C, Fabre M, Vajro P, Dommergues JP, et al. Features and outcome of autoimmune hepatitis type 2 presenting with isolated positivity for anti-liver cytosol antibody. *Clin Gastroenterol Hepatol.* 2004;2:825-30.
49. Czaja AJ, Shums Z, Binder WL, Lewis SJ, Nelson VJ, Norman GL. Frequency and significance of antibodies to chromatin in autoimmune hepatitis. *Dig Dis Sci.* 2003;48:1658-64.
50. Zachou K, Rigopoulou E, Dalekos GN. Autoantibodies and autoantigens in autoimmune hepatitis: important tools in clinical practice and to study pathogenesis of the disease. *J Autoimmune Dis.* 2004;1:2.
51. Csepregi A, Nemesánszky E, Luettig B, Obermayer-Straub P, Manns MP. LKM3 autoantibodies in hepatitis C cirrhosis: a further phenomenon of the HCV-induced autoimmunity. *Am J Gastroenterol.* 2001;96: 910-1.
52. Geller SA. Autoimmune hepatitis: Histopathology. *Clin Liver Dis.* 2014;3:19-23.
53. Feld JJ, Dinh H, Arenovich T, Marcus VA, Wanless IR, Heathcote EJ. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. *Hepatology.* 2005;42:53-62.
54. Tiniakos DG, Brain JG, Bury YA. Role of histopathology in autoimmune hepatitis. *Dig Dis.* 2015;33:53-64.
55. Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: an update. *Hepatology.* 2008;47:2089-111.
56. Abboud RT, Nelson TN, Jung B, Mattman A. Alpha1-antitrypsin deficiency: a clinical-genetic overview. *Appl Clin Genet.* 2011;4:55-65.
57. Mieli-Vergani G, Vergani D. Autoimmune paediatric liver disease. *World J Gastroenterol.* 2008;14:3360-7.
58. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology.* 2010;51:2193-2213.
59. Vergani D, Mieli-Vergani G. Pharmacological management of autoimmune hepatitis. *Expert Opin Pharmacother.* 2011;12:607-13.
60. Vergani D, Longi MS, Bogdanos DP, Ma Y, Mieli-Vergani G. Autoimmune hepatitis. *Semin Immunopathol.* 2009;31:421-35.
61. Della Corte C, Sartorelli MR, Sindoni CD, Girolami E, Giovannelli L, Comparcola D, et al. Autoimmune hepatitis in children: an overview of the disease focusing on current therapies. *Eur J Gastroenterol Hepatol.* 2012;24:739-46.
62. Kanzler S, Gerken G, Löhr H, Galle PR, Meyer zum Buschenfelde KH, Lohse AW. Duration of immunosuppressive therapy in autoimmune hepatitis (AIH). *J Hepatol.* 2001;34:354-5.
63. Lohse AW, Mieli-Vergani G. Autoimmune hepatitis. *J Hepatol.* 2011; 55:171-82.
64. Kerker N, Annunziato RA, Foley L, Schmeidler J, Rumbo C, Emre S, et al. Prospective analysis of nonadherence in autoimmune hepatitis: a common problem. *J Pediatr Gastroenterol Nutr.* 2006;43:629-34.
65. Csepregi A, Röcken C, Treiber G, Malfertheiner P. Budesonide induces complete remission in autoimmune hepatitis. *World J Gastroenterol.* 2006;12:1362-6.
66. Woynarowski M, Nemeth A, Baruch Y, Koletzko S, Melter M, Rodeck B, et al. Budesonide versus prednisone with azathioprine for the treatment of autoimmune hepatitis in children and adolescents. *J Pediatr.* 2013; 163:1347-53.
67. Parker R, Oo YH, Adams DH. Management of patients with difficult autoimmune hepatitis. *Therap Adv Gastroenterol.* 2012;5:421-37.
68. Aw MM, Dhawan A, Samy M, Bargiota A, Mieli-Vergani G. Mycophenolate mofetil as rescue treatment for autoimmune liver disease in children: a 5-year follow up. *J Hepatol.* 2009;51:156-60.
69. Schramm C, Lohse AW. Role of mycophenolate mofetil in the treatment of autoimmune hepatitis. *J Hepatol.* 2011;55:510-1.
70. Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. *Gut.* 2011;60:1611-29.
71. Alvarez F, Ciocca M, Cañero-Velasco C, Ramonet M, de Davila MT, Cuarterolo M, et al. Short-term cyclosporine induces a remission of autoimmune hepatitis in children. *J Hepatol.* 1999;30:222-7.
72. Tannous MM, Cheng J, Muniyappa K, Farooq I, Bharara A, Kappus M, et al. Use of tacrolimus in the treatment of autoimmune hepatitis: a single centre experience. *Aliment Pharmacol Ther.* 2011;34:405-7.
73. Agel BA, Machicao V, Rosser B, Satyanarayana R, Harnois DM, Dickson RC. Efficacy of tacrolimus in the treatment of steroid-refractory autoimmune hepatitis. *J Clin Gastroenterol.* 2004;38:805-9.
74. Larsen FS, Vainer B, Eefsen M, Bjerring PN, Adel Hansen B. Low-dose tacrolimus ameliorates liver inflammation and fibrosis in steroid-refractory autoimmune hepatitis. *World J Gastroenterol.* 2007;13:3232-6.
75. Peña R, Almanza E, Vargas E, Zaragoza GR, Espinosa P, Castañeda RA, et al. Vasculitis gastrointestinal en una adolescente con lupus eritematoso sistémico y síndrome antifosfolípido catastrófico. *Endoscopia.* 2016; 28:174-7.
76. Barth E, Clawson J. A Case of autoimmune hepatitis treated with rituximab. *Case Rep Gastroenterol.* 2010;4:502-9.
77. Burak KW, Swain MG, Santodomingo-Garzon T, Lee SS, Urbanski SJ, Aspinall AI, et al. Rituximab for the treatment of patients with autoimmune hepatitis who are refractory or intolerant to standard therapy. *Can J Gastroenterol.* 2013;27:273-80.
78. Silva LC, Ortigosa LC, Benard G. Anti-TNF- agents in the treatment of immune-mediated inflammatory diseases: mechanisms of action and pitfalls. *Immunotherapy.* 2010;2:817-33.
79. Efe C, Purnak T, Ozaslan E. Anti TNF-alpha therapy can be a novel treatment option in patients with autoimmune hepatitis. *Aliment Pharmacol Ther.* 2010;32:115; author reply 116-7.

80. Umekita K, Miyauchi S, Ueno S, Takajo I, Kusumoto K, Hasuike S, et al. Improvement of rheumatoid arthritis and autoimmune hepatitis in a patient treated with the tumor necrosis factor inhibitor, etanercept. *Intern Med.* 2011;50:1245-9.
81. Coffin CS, Fraser HF, Panaccione R, Ghosh S. Liver diseases associated with anti-tumor necrosis factor- α (TNF- α) use for inflammatory bowel disease. *Inflamm Bowel Dis.* 2011;17:479-84.
82. Hirano F, Tanaka H, Makino Y, Okamoto K, Makino I. Effects of ursodeoxycholic acid and chenodeoxycholic acid on major histocompatibility complex class I gene expression. *J Gastroenterol.* 1996;31:55-60.
83. Czaja AJ, Carpenter HA, Lindor KD. Ursodeoxycholic acid as adjunctive therapy for problematic type 1 autoimmune hepatitis: a randomized placebo-controlled treatment trial. *Hepatology.* 1999;30:1381-6.
84. Reardon J, Hussaini T, Alsahafi M, Azalgar VM, Erb SR, Partovi N, et al. Ursodeoxycholic acid in treatment of non-cholestatic liver diseases: A systematic review. *J Clin Transl Hepatol.* 2016;4:192-205.
85. Chai PF, Lee WS, Brown RM, McPartland JL, Foster K, McKiernan PJ, et al. Childhood autoimmune liver disease: indications and outcome of liver transplantation. *J Pediatr Gastroenterol Nutr.* 2010;50:295-302.
86. Duclos-Valleé JC, Sebah M, Rifai K, Johanet C, Ballot E, Guettier C, et al. A 10 year follow up study of patients transplanted for autoimmune hepatitis: histological recurrence precedes clinical and biochemical recurrence. *Gut.* 2003;52:893-7.
87. Werner M, Wallerstedt S, Lindgren S, Almer S, Björnsson E, Bergquist A, et al. Characteristics and long-term outcome of patients with autoimmune hepatitis related to the initial treatment response. *Scand J Gastroenterol.* 2010;45:457-67.
88. Mieli-Vergani G, Vergani D. Autoimmune hepatitis. *Nat Rev Gastroenterol Hepatol.* 2011;8:320-9.
89. Ilyas JA, O'Mahony CA, Vierling JM. Liver transplantation in autoimmune liver diseases. *Best Pract Res Clin Gastroenterol.* 2011;25:765-82.
90. Aizawa Y, Hokari A. Autoimmune hepatitis: current challenges and future prospects. *Clin Exp Gastroenterol.* 2017;10:9-18.
91. Liberal R, de Boer YS, Andrade RJ, Bouma G, Dalekos GN, Floreani A, et al. Expert clinical management of autoimmune hepatitis in the real world. *Aliment Pharmacol Ther.* 2017;45:723-732.
92. Longhi MS, Hussain MJ, Kwok WW, Mieli-Vergani G, Ma Y, Vergani D. Autoantigen-specific regulatory T cells, a potential tool for immune-tolerance reconstitution in type-2 autoimmune hepatitis. *Hepatology.* 2011;53:536-47.
93. Grant CR, Liberal R, Holder BS, Cardone J, Ma Y, Robson SC, et al. Dysfunctional CD39(POS) regulatory T cells and aberrant control of T-helper type 17 cells in autoimmune hepatitis. *Hepatology.* 2014;59:1007-15.
94. Czaja AJ. Emerging treatments for autoimmune hepatitis. *Curr Pharm Des.* 2011;17:3120-40.