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 autoimmune. Hepatopatía crónica. Hepatitis seronegative.
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-microsomal 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 T1AH.

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-globulins.

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 disease.5

Genetic factors

Genetic susceptibility is partially determined by the presence of specific molecules of class II major histocompatibility complex (MHC II), and more directly, to the human leukocyte antigen (HLA). 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).6-18

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 unknown.

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 lymphocytes.

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. 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 damage. 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 AH.

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 children

<table>
<thead>
<tr>
<th></th>
<th>Type 1 AH</th>
<th>Type 2 AH</th>
</tr>
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<tbody>
<tr>
<td>Predominant age</td>
<td>Adolescence</td>
<td>Schoolchildren and preschoolers</td>
</tr>
<tr>
<td>Typical onset</td>
<td>Chronic and insidious</td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td>Cirrhosis at diagnosis</td>
<td>Frequent</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Hypergammaglobulinemia</td>
<td>++++</td>
<td>+/+</td>
</tr>
<tr>
<td>Biliary lesions</td>
<td>Possible</td>
<td>Absent</td>
</tr>
<tr>
<td>Extrahepatic manifestations</td>
<td>Arthritis</td>
<td>Graves’ disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autoimmune purpura</td>
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<tr>
<td></td>
<td></td>
<td>Autoimmune thyroiditis</td>
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<tr>
<td></td>
<td></td>
<td>Vitiligo</td>
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<td></td>
<td></td>
<td>Alopecia</td>
</tr>
<tr>
<td>Typical antibodies</td>
<td>ANA</td>
<td>LKM-1</td>
</tr>
<tr>
<td>Other antibodies</td>
<td>SLA/LP</td>
<td>LC-1</td>
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</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Total number of patients/controls (number of children)</th>
<th>Assessed HLA</th>
<th>Conclusions</th>
</tr>
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<tbody>
<tr>
<td>Fortes et al.⁵⁵</td>
<td>41/111 (13)</td>
<td>HLA-A, -B, -C, -DR and DQ</td>
<td>No significant differences regarding HLA-A and -C were found between groups. For HLA class I, an increase in the frequency of B<em>08, B</em>18, B<em>45 and B</em>50 was observed. HLA B<em>40 was more frequent in healthy controls. For HLA class II, an increase in the frequency of HLA-DQB1</em>02, -DQB1<em>04, HLA-DRB1</em>03, DRB1<em>13 and DRB2 was observed. HLA-DRB1</em>1301 and -DRB1*0301 were the most frequent in children</td>
</tr>
<tr>
<td>Fainboim et al.⁶⁶</td>
<td>52/197</td>
<td>HLA-A, -B, -C, -DR and -DQ</td>
<td>No significant associations with HLA class I antigens were found. The HLA-DRB1 group (HLA-DRB1) was the most frequent, mainly HLA-DRB1<em>1301. HLA-DQ analysis showed an association with HLA-DQB1</em>0603</td>
</tr>
<tr>
<td>Pando et al.⁷⁷</td>
<td>206/208 (122)</td>
<td>HLA-DR and -DQ</td>
<td>The frequencies of HLA-DRB1<em>1301, -DRB1</em>0301, -DQA1<em>0103, -DQB1</em>0603 increased significantly in patients with AH. HLA-DRB1<em>1301 was associated with earlier age at disease onset; this allele is associated with AH in children. HLA-DRB1</em>1302 works as a protection factor</td>
</tr>
<tr>
<td>Bittencourt et al.⁸⁸</td>
<td>139/129 (74)</td>
<td>HLA-DRB and -DQB1</td>
<td>In patients with type 1 AH, there was a significant increase in the HLA-DRB1<em>13, -DRB1</em>03, -DRB3 and -DQB1<em>06 alleles. HLA-DRB1</em>13 was more frequent in children than in adults. The low frequency of HLA-DQB1<em>0301 can indicate a protective role of this allele; In type 2 AH, a significant increase in DRB1</em>07, DRB1<em>03, DRB4y DQB1</em>02 was observed</td>
</tr>
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</table>

HLA, human leukocyte antigen; AH, autoimmune hepatitis
necrosis factor family and induces apoptosis through binding of its ligand (FasL/CD95L)\textsuperscript{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-\(\alpha\)). 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 triggers\textsuperscript{27-30}.

**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\textsuperscript{7,9,31-34}.

**Associated autoimmune diseases**

Forty-percent of patients with AH has an associated autoimmune disease\textsuperscript{35}. 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 polyglandular\textsuperscript{35-41}. 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)\textsuperscript{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 treatment\textsuperscript{43-45}.

**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\textsuperscript{42,27}.

**Autoantibodies**

Its detection constitutes an important diagnostic tool that allows classification in the various types of AH (Table 4)\textsuperscript{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 damage\textsuperscript{52}.

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 criteria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA or SMA</td>
<td>Greater than or equal 1:40</td>
<td>1</td>
</tr>
<tr>
<td>ANA or SMA</td>
<td>Greater than or equal 1:80</td>
<td>2</td>
</tr>
<tr>
<td>Anti LKM-1</td>
<td>Greater than or equal 1:40</td>
<td>2</td>
</tr>
<tr>
<td>Anti SLA/LP</td>
<td>Positive</td>
<td>2</td>
</tr>
<tr>
<td>Immunoglobulin G</td>
<td>Above the normal upper limit</td>
<td>1</td>
</tr>
<tr>
<td>Liver histology</td>
<td>&gt;1.10 the normal value</td>
<td>2</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>Compatible with AH</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Typical AH (Interface hepatitis)</td>
<td>2</td>
</tr>
</tbody>
</table>

≥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

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clinical significance</th>
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| 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  
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) | 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\textsuperscript{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\textsuperscript{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 decrease 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\textsuperscript{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\textsuperscript{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 a 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 steroids\textsuperscript{61}.

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 phases\textsuperscript{62}.

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 necessary\textsuperscript{63}.

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 recommended\textsuperscript{68}.

**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 treatment\textsuperscript{64}. The presence of cirrhosis at the onset of treatment increases the risk of treatment failure\textsuperscript{53}.

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 agent. 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 remission. 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 day.

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 azathioprine. Although mycophenolate seems to be a promising agent that is especially useful as rescue therapy in difficult patients, a significant disadvantage is its high cost.

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.

Tacrolimus leads to inhibition of the synthesis of cytokines (IL-2, IL-3 and interferon-alpha), 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 nephrotoxicity.

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 AH.

Infliximab, etanercept, and adalimumab are anti-TNF agents commonly used for the treatment of immune-mediated diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease. 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-TNF antibodies. Future studies would have to define the role of anti-TNF 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. 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 steroids.

### Liver transplantation

AH represents 2-3% of the indications for liver transplant in pediatric patients. 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 later. Long-term steroid therapy is recommended in patients that have had a liver transplant due to AH. Post-transplant survival in AH is good, with 5-year survival rates of up to 90-95%.

### 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.\textsuperscript{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.\textsuperscript{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 disease.\textsuperscript{94}

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

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References


