

- a. National Committee of Hepatology, Sociedad Argentina de Pediatría.
- b. Universidad Mayor de San Andrés, Hospital del Seguro Social Universitario, Bolivia.
- c. High-Specialty Medical Unit, Children's Hospital, Centro Médico Nacional de Occidente, Mexican Institute of Social Security (Instituto Mexicano del Seguro Social, IMSS), Guadalajara, México.
- d. Hospital de Niños Sor María Ludovica, La Plata, Argentina.
- e. Hospital Italiano de Buenos Aires, Argentina.
- f. Fundación Valle del Lili, Cali, Colombia.
- g. Hospital de Pediatría Prof. Dr. Juan P. Garrahan, the City of Buenos Aires, Argentina.
- h. Hospital Clínico San Borja Arriarán, Santiago, Chile.
- i. Centro Médico UGANEP, Bucaramanga, Colombia.
- j. Hospital Infantil de Córdoba, Argentina.
- k. Hospital Alemán and Hospital El Cruce. Buenos Aires, Argentina.
- l. Instituto Nacional de Salud del Niño-San Borja. Perú.
- m. Hospital Universitario de Puebla, Benemérita Universidad Autónoma de Puebla, México.
- n. Hospital Alemán de Buenos Aires, Argentina.

*E-mail address:*

Margarita Ramonet:  
margarita.ramonet@gmail.com

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## Autoimmune hepatitis in pediatrics, a review by the Working Group of the Latin American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Margarita Ramonet<sup>a</sup>, Nelson Ramirez-Rodriguez<sup>b</sup>, Felipe Álvarez Chávez<sup>c</sup>, María C. Arregui<sup>d</sup>, Gustavo Boldrini<sup>e</sup>, Verónica Botero Osorio<sup>f</sup>, Miriam Cuarterolo<sup>g</sup>, Marcela Godoy<sup>h</sup>, Fernando Alonso Medina Monroy<sup>i</sup>, Gabriela Oropeza<sup>j</sup>, Rosana Pérez Carusi<sup>k</sup>, Diana Pérez Rodríguez<sup>l</sup>, Fátima Azereth Reynoso-Zarzosa<sup>m</sup>, Mirta Ciocca<sup>n</sup>

### ABSTRACT

Autoimmune hepatitis (AIH) is a chronic inflammatory condition of the liver characterized by a complex interaction among genetic factors, immune response to antigens present in hepatocytes, and immune regulation alterations. Its distribution is global and there is a female predominance. AIH is divided into 2 groups, depending on the type of serum autoantibodies detected. The most common presentation is acute hepatitis (40%), with non-specific symptoms, high aminotransferase levels, and hypergammaglobulinemia. Standard treatment consists of the administration of immunosuppressive drugs. It is a complex condition, often difficult to diagnose. If not managed adequately, the 5-year mortality rate may reach 75%.

**Key words:** autoimmune hepatitis, pediatrics, treatment.

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### INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory condition of the liver characterized by a complex interaction among genetic factors, immune response to antigens present in hepatocytes, and immune regulation alterations. Depending on the serological profile, AIH is divided into two subtypes: type 1, positive for smooth muscle antibodies (SMA) and/or antinuclear antibodies (ANA), and type 2, positive for liver kidney microsomal antibody type 1 (anti-LKM-1) and/or anti-liver cytosol type 1 (anti-LC-1).<sup>1,2</sup>

AIH distribution is global and there is a female predominance, with a ratio of 3:1 for type 1 and up to 9:1 for type 2. Incidence peaks are between 10 and 11 years old for AIH type 1 and between 6 and 7 years old for AIH type 2; the latter being predominant in the pediatric age group.<sup>2,3</sup>

The course of AIH is progressive and advances to cirrhosis with end-stage liver failure if left untreated.<sup>3</sup>

### PATHOPHYSIOLOGY

There is evidence that, in individuals with a genetic predisposition, exposure to triggering factors leads to an imbalance between effector and regulatory immunity in a particular autoimmune ecosystem. After said exposure, deficiencies or disruptions in homeostatic mechanisms have been described that

can overcome self-tolerance making autoimmune aggression in the liver to persist even in the absence of the initial trigger. This is due to the existence of “molecular mimicry” mechanisms and a reduction in the number and function of regulatory T cells (Tregs).<sup>2-6</sup>

Genetic susceptibility is determined by the presence of major histocompatibility complex class II (MHC II) molecules, more specifically human leukocyte antigen (HLA) DR locus, located in the short arm of chromosome 6. Depending on the ancestry or geographic region, HLA susceptibility varies. Alleles conferring susceptibility to type 1 AIH are HLA-DR3 and DR4 (DRB1\*0301 and DRB1\*0401) among European and North American individuals, and DRB1\*1301 among pediatric patients in South America.<sup>2,4,7,8</sup> In relation to type 2 AIH, the most common allele among German Caucasian patients is DRB1\*07 and HLA haplotype DRB1\*15-DQB1\*06.<sup>9</sup> In Brazil, the alleles predisposing to type 2 AIH are DRB1\*07 and DRB1\*03; however, these studies are limited due to the low frequency of this condition.<sup>10</sup>

The immune response consists of an aberrant activation of liver dendritic cells and the subsequent disruption of immune homeostasis. The inflammatory reaction is caused by T cells (mainly T helper cells), B cells, macrophages, and natural killer (NK) cells. The triggering factor of the inflammatory response is still unclear. Malfunctioning and a decrease of regulatory T cells could be an explanation, as there is an increase in Tregs during effective treatment. These cells suppress cytokine response and proliferation in CD4+ and CD8+ effector cells and reduce the functions of macrophages, dendritic cells, NK cells, and B cells.<sup>2-7</sup>

Tregs play a critical role in the maintenance of immune homeostasis and the prevention of autoimmune diseases, which may provide a potential therapeutic target for this condition. However, the role of Tregs in AIH has not been defined yet. A review analyzed studies related to Tregs in several animal models.<sup>11</sup>

The cytotoxic T lymphocyte antigen-4 (CTLA-4), the FOXP3 regulatory transcription factor, and the cell adhesion molecule CD62 are cell surface markers involved in anti-inflammatory mechanisms. The number of NK T cells is reduced in AIH patients; this causes lower levels of interleukin (IL)-4 and IL-2, which results in a reduced expression of CTLA-4 in CD4+ T cells, playing a pivotal role in liver autoaggression.<sup>5,6,12,13</sup>

In the hypothesis of “molecular mimicry” and cross-reactivity between foreign epitopes and hepatic antigens, several viral agents have been included as potential triggers: hepatitis A, B, C and E viruses; measles virus; Epstein-Barr virus and herpes simplex virus. The molecular mimicry is also proposed as a potential key element for microbiome-associated and drug-induced intestinal autoimmunity.<sup>2,3,14</sup>

## DIAGNOSIS

The diagnosis of AIH is focused on a combination of clinical, biochemical, immune, and histological findings and the exclusion of other causes of liver disease.

### Clinical manifestations

In the pediatric population, AIH may present in different ways and be more aggressive than in adults. The most common presentation is acute hepatitis (approximately 40%), with non-specific symptoms, including loss of appetite, nausea, vomiting, and arthralgia, followed by jaundice, choloria and/or acholia. To a lesser extent, it may start as acute liver failure in approximately 3% and 25% of patients with AIH-1 and AIH-2, respectively.<sup>3,15,16</sup>

Other less common presentations include insidious AIH with predominantly non-specific symptoms (25-40%), complications of cirrhosis (10%), or asymptomatic AIH, diagnosed incidentally (abnormal liver function tests, hepatosplenomegaly).

Regardless of the presentation, nearly one-third of patients with AIH have cirrhosis at the time of diagnosis, which evidences the long course of this disease.<sup>3</sup> In addition, patients may have a fluctuating periods of remissions and recurrences, which may delay diagnosis and treatment initiation. It is critical to suspect AIH, confirm the diagnosis immediately, and start an early treatment.

During physical examination, patients may not have signs of underlying liver disease or show jaundice and the signs typical of chronic liver disease, including telangiectasis, palmar erythema, hepatosplenomegaly, and collateral blood flow, among others.<sup>17</sup>

A family history of autoimmune disease is common in 40% of cases, and approximately 20% of patients show associated autoimmune alterations, either at the time of diagnosis or during the course of the disease. These include thyroiditis, inflammatory bowel disease, hemolytic anemia, vitiligo, celiac disease,

insulin-dependent diabetes, etc.<sup>2,3,18</sup>

### Lab tests

The typical findings include high aminotransferase levels (2 to 50 times normal values), hypergammaglobulinemia (an increase of IgG secondary to non-specific B cell proliferation), direct hyperbilirubinemia, and normal or slightly increased gamma-glutamyl transferase (GGT) levels. Up to 45% of patients with AIH-2 and 9% of those with AIH-1 have IgA deficiency. C4a levels may be reduced in up to 69% of cases.<sup>2,3,14</sup>

In patients with cirrhosis and portal hypertension, pancytopenia secondary to hypersplenism is observed. Patients with acute liver failure usually have a prolonged prothrombin time that does not respond to vitamin K administration.

### Autoantibodies

A key element in AIH diagnosis is autoantibody detection; however, they may also be present in other conditions, and their isolated finding is not enough to confirm the diagnosis.<sup>2-19</sup>

Standard serology includes autoantibody detection by immunofluorescence, which allows to differentiate between both types of AIH:

- AIH-1 is characterized by the presence of ANA and/or SMA.
- AIH-2 is characterized by the presence of anti-LKM-1 and/or anti-LC-1 antibodies.

It has been suggested that there is a third group characterized by the presence of antibodies to soluble liver antigen (SLA) or liver pancreas antigen, which are currently included in AIH-1.<sup>3,14</sup>

Overall, 40% of AIH-1 cases and 80% of AIH-2 cases are diagnosed before 18 years old.<sup>2,3,14,15</sup>

In the pediatric population,  $\geq 1:20$  dilutions for ANA and SMA, and  $\geq 1:10$  dilutions for anti-LKM-1 are indicative of disease.<sup>2,18</sup>

There is a seronegative form of AIH, present in approximately 10% of cases, which should be taken into consideration once other potential etiologies are ruled out based on patient age.

### Histology

A liver biopsy is important for the diagnostic confirmation and allows to assess the severity of liver injury.

Interface hepatitis consists of an invasion of the limiting plates (hepatocytes surrounding the portal space) by the lymphoplasmacytic infiltrate (made up of T, B, and plasma cells), which extends to the lobule. This is a histological

feature of interface hepatitis, although not exclusive of it.<sup>2,19</sup> Plasma cells are usually abundant in the interface and the lobule, but their scarcity in the inflammatory infiltrate does not rule out the diagnosis. Emperipolesis is the capacity of lymphocytes, plasma cells, and polymorphonuclear cells to penetrate the cytoplasm of other cells; both maintain viability in 65% of cases. This is not a specific sign of AIH either.<sup>2</sup> Histological signs suggestive of disease progression are panlobular hepatitis, bridging necrosis, and massive necrosis. Cirrhosis is present in 40-80% of children at the time of diagnosis.<sup>2,3,19-21</sup> Patients with liver failure may develop massive hepatic necrosis.<sup>2</sup>

### Diagnostic scoring system

The International Autoimmune Hepatitis Group has proposed and developed a scoring system for scientific purposes, which was then simplified by the same group. Both scores have been implemented in the adult population. The simplified score showed a moderate sensitivity (77%) and a high specificity (95%) for the diagnosis of AIH in children<sup>19,21-25</sup> (Table 1).

### Differential diagnoses

AIH is not accompanied by clinical, laboratory, or histological pathognomonic findings. For this reason, several parameters are required to guide diagnosis and exclude other conditions, such as chronic viral hepatitis B and C, Wilson's disease, alpha-1 antitrypsin deficiency, and the intake of toxic substances. In patients with acute presentation, other hepatotropic viruses should be excluded, including hepatitis A and E, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, parvovirus B19, and adenovirus.<sup>2,18,22</sup>

The approach to a potential AIH diagnosis should consider an association between AIH-1 and sclerosing cholangitis, a condition known as "autoimmune sclerosing cholangitis" or "overlap syndrome". This is characterized by the presence of humoral parameters of cholestasis and signs of bile duct involvement in magnetic resonance cholangiography.<sup>2,3,22,26</sup>

### Prognosis

AIH is a complex condition, sometimes difficult to diagnose due to its dormant symptoms in children, on occasions with a very aggressive course. If not treated adequately, the 5-year mortality may reach 75%.<sup>3</sup>

With an adequate management of immunosuppression, the response is successful. Treatment is usually prolonged.<sup>2,19</sup>

Liver transplantation is indicated for patients who develop advanced liver disease despite immunosuppressive therapy, and for those with fulminant liver failure.<sup>2,26,27</sup>

## TREATMENT

Treatment consists of the administration of immunosuppressors in order to control the liver inflammatory process.

Disease resolution is defined as the normalization of clinical, biochemical, immune, and histological parameters. The combination used is prednisone or prednisolone, at a dose of 2 mg/kg/day (maximum: 60 mg/day) plus azathioprine at a dose of 1.5-2 mg/kg/day.<sup>2,3</sup> In 95% of cases, aminotransferase levels return to normal levels within 6 months after treatment initiation. Immune remission may be slower. Patients with cirrhosis may continue with increased IgG levels.<sup>23</sup> The histological response occurs later than the biochemical response, but a liver biopsy is not indicated to confirm it.<sup>2</sup> Less than 10% of patients have an incomplete response to treatment (improvement of biochemical parameters), but do not meet all of the above

mentioned criteria for remission.<sup>3</sup>

Sometimes, patients develop adverse effects that prevent them from continuing with treatment. In other circumstances, treatment failure implies a lack of improvement in biochemical parameters despite good adherence.

High steroid doses required at treatment initiation may cause moderate to severe adverse effects, which may lead to poor adherence among adolescent patients. Adverse effects of azathioprine are less common. As clinical and biochemical parameters improve, it is critical to gradually reduce the steroid dose. The main purpose of treatment is to reach the minimum necessary doses to maintain remission and prevent adverse effects in the long term.

Cyclosporine is used in patients who fail to respond or who have an incomplete response to standard treatment or in those who do not tolerate it. Cyclosporine has proven to be effective and has mild and transient adverse effects during long-term follow-up.<sup>26-31</sup>

Tacrolimus is another treatment option, with similar indications and usage as cyclosporine. The budesonide and azathioprine combination may be effective in patients without cirrhosis, with fewer unwanted effects than prednisone. Mycophenolate mofetil may be used in patients

TABLE 1. Simplified criteria for the diagnosis of autoimmune hepatitis

Parameter	Result	Score
Autoantibodies:		
ANA or SMA	≥ 1/40	+1
ANA or SMA	≥ 1/80	+2
LKM1	≥ 1/40	+2
SLA	Positive	+2
No antibodies	None	0
IgG		
	Upper limit	+1
	> 1.10 times the upper limit of normal	+2
		0
Histological findings		
	Compatible	+1
	Typical	+2
	Not compatible	0
Markers of viral hepatitis		
	Absent	+2
	Present	0

Probable diagnosis: AIH ≥ 6; definite diagnosis: AIH ≥ 7.

IgG: immunoglobulin G; ANA: antinuclear antibodies; SMA: smooth muscle antibodies; LKM1: liver-kidney microsomal antibody type 1; SLA: soluble liver antigen.

Adapted from: Hennes E, et al.<sup>2</sup>



intolerant to azathioprine. Infliximab, an anti-tumor necrosis factor (anti-TNF), and rituximab, a monoclonal antibody against B cell surface receptor (anti-CD20), are potential treatment options, but data about their use are still insufficient.<sup>32-34</sup>

Disease relapse, determined by an increase in aminotransferase levels, with or without symptom recurrence, may occur after complete remission, either due to treatment discontinuation or poor treatment adherence. The reintroduction of immunosuppressive therapy is usually effective to reach remission once again, without long-term effects.

In patients with acute liver failure and encephalopathy or who develop advanced liver disease despite immunosuppressive therapy (2-3%), the treatment of choice is liver transplantation, with a 91% and 84% rate of survival at 1 year and 5 years, respectively. AIH recurrence may occur in up to 40% of children who underwent liver transplantation.<sup>35-37</sup>

### Treatment discontinuation

AIH shows a good response to immunosuppressive therapy; the frequency of relapse following treatment discontinuation in pediatrics is 45-80%.<sup>2,3</sup> This exposes patients to a risk for higher immunosuppressive therapy doses and disease progression.

A minimum of 2 years of complete and sustained remission (normal ALT, AST, and IgG levels) is required prior to proposing treatment discontinuation, and the recommended minimum treatment is 2-3 years.<sup>2,37,38</sup>

Some authors include immunofluorescence antibody titers below 1:20 (ANA, SMA).<sup>2</sup> A liver biopsy is indicated prior to the discontinuation of immunosuppressive therapy because residual inflammation may anticipate relapse, even with normal biochemical parameters. Based on this protocol, some studies demonstrated that it is possible to withdraw medication in only 20% of patients with AIH-1, and in no patients with AIH-2.<sup>2</sup>

Patient follow-up should be regular and lifelong, even after treatment discontinuation and despite remission is maintained.

### FOLLOW-UP AND TRANSITION

Clinical follow up should check whether children are exercising regularly,<sup>38</sup> and are

receiving calcium (1000-1500 mg / day) and vitamin D (1000 IU / day) to prevent osteoporosis secondary to prednisone administration. Bone mineral density should be assessed at treatment initiation and then annually.<sup>20,39</sup>

It is recommended to check the immunization schedule, especially the hepatitis A and B vaccines and the flu vaccine every year.<sup>40</sup>

Patients who discontinue immunosuppressive therapy should have their AST, ALT, IgG, and autoantibody levels measured every 3 months for at least 5 years.<sup>2,3</sup>

Advances in the management of chronic liver disease in children have allowed their survival into adult age, with or without their native liver. The transition from pediatric to adult medical care requires the adult health care team to have knowledge about AIH. The ideal age for transition to an adult specialist is between 18 and 21 years.<sup>41</sup>

It is critical that each site has a transition program in place so that both children and their parents feel supported, have their questions answered, and that there is continuity in the management by the new treatment team.

### CONCLUSIONS

- AIH is an immune-mediated inflammatory liver disease of unknown etiology. It may develop in both males and females and in people of any age and ethnicity, although it predominates during prepubertal stage.
- AIH is diagnosed based on the clinical condition, high aminotransferase levels, the presence of serum autoantibodies, high IgG levels, and compatible histological findings.
- Conventional treatment consists of prednisone or prednisolone, at an initial dose of 2 mg/kg/day (maximum: 60 mg/day) plus azathioprine at a dose of 1.5-2 mg/kg/day.
- Liver transplantation is a therapeutic resource for patients with acute liver failure or liver disease progression in spite of immunosuppressive therapy. ■

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