J Pediatr (Rio J). 2019;95(4):382–384

Jornal de Pediatria

www.jped.com.br

EDITORIAL

# Autoimmune hepatitis in children☆,☆☆

## Hepatite autoimune em crianças

**Fernando Alvarez**

*Centre Hospitalier Universitaire Sainte-Justine (CHU-Sainte Justine), Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Montréal, Canada*

Autoimmune hepatitis (AIH) is an inflammatory disease of the liver, secondary to a loss of immune tolerance against liver antigens resulting in a progressive destruction of the hepatic parenchyma.[1] The article from Porta et al. in the present issue describes the clinical, laboratory, and histologic features of a large cohort of children with AIH, and includes an analysis of the treatment response and outcome.[2] This multicenter study presents the results of a retrospective revision of medical records from 828 children, representing the largest series in the world literature.

A main characteristic of AIH is its fluctuant course, partially explaining the delay between the first symptoms or signs and the diagnosis of the disease, delaying the beginning of the immunosuppressive treatment, thus increasing the risk of developing cirrhosis and liver failure.[1] In the present series, the time recorded between onset and diagnosis was 11 and 15 months for AIH type 1 and type 2, respectively. To avoid such delay, AIH should be included in the differential diagnosis of any liver anomaly, from fortuitous discovery of high serum aminotransferases to signs of chronic liver disease, keeping in mind that spontaneous partial improvement of clinical or laboratory signs can occur in the course of the disease. Clearly shown in Table 2 of the Porta et al.[2] article, a normal serum ALT/AST level does not eliminate the diagnosis of AIH. Mainly in adolescents, a normal or slight increase of ALT/AST is associated with a mild inflammation in the liver biopsy.[3]

Acute hepatitis is the most frequent presentation of AIH, although in some cases advanced fibrosis is already present in the liver biopsy, indicating a previous subclinical evolution.[1–4] In this cohort, more than half of the children showed acute hepatitis, in either AIH type 1 or type 2. In addition, more than one-third showed signs of hepatic failure, and in 3.6%–10% of children had fulminant hepatitis. The liver function is more frequently affected at diagnosis in children with AIH type 2.[5,6]

In the follow-up of the reported patients, cholangiography was performed in patients with high GGT during monitoring of the disease or in those not responding to treatment. This is not the best approach; it would be more appropriate to look for abnormal bile ducts (sclerosing cholangitis) at the diagnosis in all the children with AIH type 1, with serum GGT > 7–10× normal values, and/or neo-ductular proliferation at the liver biopsy, peri-ductular fibrosis, or damage of the biliary epithelium. It should also be considered that 10–15% of children with signs of AIH could have ''small ducts sclerosing cholangitis,'' in which only histologic anomalies of the bile duct are recorded but the cholangiography does not show anomalies in the large bile ducts.[1,7]

DOI of original article:
https://doi.org/10.1016/j.jped.2018.04.007

☆ Please cite this article as: Alvarez F. Autoimmune hepatitis in children. J Pediatr (Rio J). 2019;95:382–4.

☆☆ See paper by Porta et al. in pages 419–27.

*E-mail:* fernando.alvarez@umontreal.ca

https://doi.org/10.1016/j.jped.2018.08.001

Extra-hepatic autoimmune diseases are present in more than 20% of the patients at diagnosis; even if they are very young, as shown by Porta et al.[2] Autoimmune diseases are also found in first-degree relatives, in similar proportions. Furthermore, in the initial investigation of children with AIH it is necessary to look for the more frequent extra-hepatic autoimmune diseases, mainly those influencing the choice of the immunosuppressive drug to be prescribed. In children with diabetes, prednisone should not be the first choice, while cyclosporine should be avoided in children with glomerulonephritis.[1]

The possibility of AIH must also be suspected in children with increased liver enzymes who have any extra-hepatic autoimmune disease. Bowel inflammation in celiac disease or inflammatory bowel diseases, as Crohn's disease or ulcerative colitis, frequently shows an increase of serum aminotransferases at diagnosis. In most cases, increases of ALT/AST levels are mild or moderate, and normalize after the beginning of treatment. Such increases are the result of activated T cells trapped in the liver and dying by apoptosis, the so-called bystander hepatitis.[8] However, in some of these children abnormal liver tests are the manifestation of AIH, requiring specific treatment. AIH patients share HLA alleles of susceptibility, and IgA deficiency with celiac disease patients, as well as with other autoimmune diseases.[9]

The incidence of cirrhosis was relatively low in the reported population; this could be due to the fact that 20% of patients did not have a liver biopsy, and the reasons why it was not carried out were not described. The presence of a hepatic failure could preclude the liver biopsy in children presenting with signs of chronic liver disease, explaining a decrease in the number of patients recorded with cirrhosis. Another possibility is a sampling error; a needle liver biopsy does not always allow the identification of nodules. In contrast, fibrosis was found in more than two-thirds of the children at the biopsy; unfortunately, the stage of fibrosis is not reported in the article. There is no pathognomonic histologic feature of AIH; however, the observation of plasmocytes in the portal tract and interface hepatitis are of great help, but its absence does not exclude the diagnosis. The fluctuant course of the inflammatory process explains this possibility.[1,3]

Circulating autoantibodies contribute to the diagnostic approach. Unfortunately, in around 10% of children with AIH these markers are absent, and the patients are classified as having a seronegative AIH.[1] In some of these children, autoantibodies are detected late in the follow-up, mostly following an episode of relapse. Seronegative AIH has not been included in the present report, but it should not be ignored, since those children show a good response to an immunosuppressive treatment. No testing for anti-liver cytosol type 1 (LC1) autoantibodies was conducted, thus excluding from this study around 10% of the children with AIH type 2 expressing only this marker.[10] The authors recognized these biases, acknowledging that the data in the article do not represent the actual prevalence of AIH in pediatric patients in Brazil.

Immunosuppressive treatment is indicated for control of the liver inflammation. Standard treatment consists of the administration of prednisone or the association of prednisone and azathioprine, usually at doses of 2 mg/kg/day and 1.5–2 mg/kg/day, respectively.[3,4,11] Other immunosuppressive drugs, such as calcineurin inhibitors or mycophenolate mofetil, are considered in patients with cortico-dependent or cortico-resistant liver inflammation, or in patients with a clinical status contra-indicating the standard therapy. Calcineurin inhibitors have also been used to induce control of the inflammation, and were later replaced by corticosteroids and azathioprine at low doses.[12] Budesonide (Entocort), a corticosteroid extracted mostly at the first passage by the liver, has been proposed as an alternative to prednisone.[13] However, the efficacy of budesonide is lower than prednisone as part of the initial therapy, therefore, it is not recommended for this use in children.[13] The goal of the treatment is to obtain a complete remission, which is evaluated as the normalization of serum ALT/AST and of plasma IgG (or gammaglobulins). In most published pediatric series, complete remission is reported to range from 80% to more than 90%. In this large cohort, the remission rate was 74.7%, relatively low for patients with AIH type 1. Many theories can be proposed to explain such results: (1) children with sclerosing cholangitis were included in the analysis, knowing that these patients do not respond well to immunosuppression; (2) sclerosing cholangitis was underdiagnosed, since cholangiography was not performed in all patients with AIH type 1; (3) doses of prednisone were lower than usually prescribed, even if this appears less probable since AIH type 2 children responded as expected.

Bilirubin levels and INR or prothrombin time are prognosis factors of the response to treatment, as well as the presence of cirrhosis.[11] Total and direct bilirubin levels and cirrhosis (fibrosis) were not statistically significant between AIH type 1 and 2, but more patients with AIH type 2 present with hepatic failure (INR > 1.5) and fulminant hepatic failure (not defined in this work). Nevertheless, children with AIH type 2 showed a better and faster response to immunosuppression. Moreover, the percentage of children needing a liver transplant was similar in AIH type 1 and type 2, but almost double the number of patients with AIH type 1 died during evolution. Prospective studies or review of the already collected data can provide some answers to these intriguing results, considering that most published work regard AIH type 2 in children as a more severe disease.

The work from Porta et al. published in this journal represents a gigantic effort, requiring strong leadership and great dedication from all the authors. Even if this study shows many minor drawbacks, due to its retrospective multicenter nature, it could be considered as a major contribution to the knowledge of AIH in children. This kind of work facilitates sharing criteria among the participants, homogenizing the diagnosis and treatment approaches, and designing prospective studies to answer many of the questions raised.

## Conflicts of interest

The author declares no conflicts of interest.

## References

1. Alvarez F. Autoimmune hepatitis and primary sclerosing cholangitis. Clin Liver Dis. 2006;10:89–107.
2. Porta G, Carvalho E, Santos JL, Gama J, Borges CV, Seixas RB, et al. Autoimmune hepatitis in 828 Brazilian children and

adolescents: clinical and laboratory findings, histological profile, treatments, and outcomes. J Pediatr (Rio J). 2019;95:419–27.
3. Maggiore G, Bernard O, Homberg JC, Hadchouel M, Alvarez F, Hadchouel P, et al. Liver disease associated with anti-liver-kidney microsome antibody in children. J Pediatr. 1986;108:399–404.
4. Maggiore G, Veber F, Bernard O, Hadchouel M, Homberg JC, Alvarez F, et al. Autoimmune hepatitis associated with anti-actin antibodies in children and adolescents. J Pediatr Gastroenterol Nutr. 1993;17:376–81.
5. Maggiore G, Porta G, Bernard O, Hadchouel M, Alvarez F, Homberg JC, et al. Autoimmune hepatitis with initial presentation as acute hepatic failure in young children. J Pediatr. 1990;116:280–2.
6. Porta G, Gayotto LC, Alvarez F. Anti-liver-kidney microsome antibody-positive autoimmune hepatitis presenting as fulminant liver failure. J Pediatr Gastroenterol Nutr. 1990;11:138–44.
7. Gregorio GV, Portmann B, Karani J, Harrison P, Donaldson PT, Vergani D, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology. 2001;33:544–53.
8. Alvarez F. The diagnosis and classification of immune-mediated hepatic diseases. In: Gershwin ME, Vierling JM, Manns MP, editors. Liver immunology: principles and practice. 2nd ed. New York, USA: Springer Science+Business Media; 2014. p. 95–109.
9. Beland K, Lapierre P, Alvarez F. Influence of genes, sex, age and environment on the onset of autoimmune hepatitis. World J Gastroenterol. 2009;15:1025–34.
10. Bridoux-Henno L, Maggiore G, Johanet C, Fabre M, Vajro P, Dommergues J-P, 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.
11. 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.
12. 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 Hepatology. 1999;30:222–7.
13. 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.