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REVIEW

Autoimmune hepatitis in childhood: The role of genetic and immune factors

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Abstract

Autoimmune hepatitis (AIH) is a rare chronic inflammatory disease of the liver, which affects a group of patients who lost their immunological tolerance to antigens of the liver. It is clinically characterized by hypergammaglobulinemia, elevated liver enzymes, presence of autoantibodies and histological changes. Although being rare in children, it represents a serious cause of chronic hepatic disease that can lead to cirrhosis and hepatic failure. Clinical findings, exclusion of more common liver disorders and the detection of antibodies antinuclear antibodies, smooth muscle antibodies and anti-LKM1 are usually enough for diagnosis on clinical practice. The pathogenic mechanisms that lead to AIH remain obscure, but some research findings suggest the participation of immunologic and genetic factors. It is not yet knew the triggering factor or factors that stimulate inflammatory response. Several mechanisms proposed partially explain the immunologic findings of AIH. The knowledge of immune factors evolved might result in better markers of prognosis and response to treatment. In this review, we aim to evaluate the findings of research about genetic and immune markers and their perspectives of application in clinical practice especially in pediatric population.

Key words: Autoimmune hepatitis; Genetics; Clinical practice; Immunophenotype

Core tip: In this review article, we reported recent data on autoimmune hepatitis in pediatric patients highlighting the importance of genetic and immune markers. We also discuss the perspectives of the application of these new biomarkers in clinical practice.

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INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory disease of the liver that is rarely found in children and adolescents. AIH affects a group of patients who have lost their immunological tolerance to antigens of

the liver[1-4]. It is more frequent in female patients and is characterized by hypergammaglobulinemia, elevated liver enzymes, the presence of autoantibodies and histological changes[4-7]. The age of onset usually ranges from months to 75 years old, but it is very rare before the age of two years old, and the highest incidence occurs between 10 and 30 years old[2]. In addition to being considered rare in children, AIH represents a serious cause of chronic hepatic disease, which can result in cirrhosis and its complications. Immunosuppressive treatment results in a good response, but a delay in or absence of treatment can result in cirrhosis and liver failure[2,6]. This condition can also be complicated by association with autoimmune cholangitis, in which bile duct disease is present together with hepatitis, particularly in children[2,7,8].

Clinical and laboratory diagnosis

Because histological activity index (HAI) is a rare disorder, one crucial point for diagnosis is the exclusion of more common pathologies. The diagnosis is confirmed by clinical findings, laboratory and histopathology tests and the exclusion of other causes of chronic liver disease[4,6,7,9]. The clinical spectrum is broad, ranging from asymptomatic laboratory abnormalities to clinical symptoms similar to fulminant acute viral hepatitis. The classical presentation is jaundice, dark urine, fever, asthenia, anorexia and increased abdominal volume in an acute or insidious presentation[6,10]. Hepatomegaly, splenomegaly and signs of chronic liver disease, such as spider veins, collateral circulation and abdominal ascites, might be present. Approximately 20% of cases are associated with other autoimmune disorders[8].

According to the presence of autoantibodies, AIH can be classified into two forms: type 1 autoimmune hepatitis, in which antinuclear antibodies (ANAs) and/or anti-smooth muscle antibodies (SMAs) are detected; and autoimmune hepatitis type 2, in which anti-liver-kidney (anti-LKM1) autoantibodies are detected[9,11-13]. In adult patients, the presence of anti-soluble liver-kidney antigen and anti-liver-pancreas might be understood as a third form of AIH (AIH type 3), despite clinical features similar to type 1[14]. Type 1 is the most common type of AIH in any age group, while type 2 usually occurs in younger patients, with courses having a greater likelihood of acute liver failure[2,3].

During treatment, ANA and SMA levels can decrease, but neither level seems to have a correlation with prognosis[15-17]. Therefore, 10%-15% patients are negative for ANAs, SMAs and LKM-1 at clinical presentation but later show detectable levels of these autoantibodies, with only five percent remaining negative over time[15,18]. Other autoantibodies could facilitate in diagnosis and/or act as prognostic markers, and their possible clinical applications are listed in Table 1[19-38].

Most services do not perform routine assessment of the autoantibodies shown in Table 1, which remain reserved for research situations. The antibodies ANA, SMA and anti-LKM1 are usually sufficient for diagnosis in clinical practice. More research is needed to establish the clinical use of these autoantibodies and to investigate the presence of these autoantibodies in pediatric patients, thereby elucidating their role in this group of patients.

Diagnostic criteria

The International Autoimmune Hepatitis Group diagnostic criteria for AIH, published in 1993 and revised in 1999, guide diagnosis and facilitate early treatment[39-41]. A simplified scoring system, created in 2008, considers transaminases levels, autoantibodies, immunoglobulin G levels, liver biopsy, exclusion of Wilson disease and of viral hepatitis and cholangiogram[41,42]. The use of these criteria could also be helpful in children, but limitations must be recognized[43]. In children, it is difficult to differentiate AIH from primary sclerosing cholangitis or to identify autoimmune cholangitis overlap syndrome. The diagnosis of fulminant hepatitis cases has not been well determined because the use of 1/40 as a titer for autoantibodies is high to use in children (1/20 for ANA and SMA and 1/10 for anti-LKM1 are considered positive in this age group)[3,43]. For these reasons, histology is often included in the diagnostic criteria for HAI in children[3,44]. On histological examination, characteristic findings include the presence of piecemeal necrosis (interface hepatitis), lymphoplasmocytic infiltrates with numerous plasmocytes, and rosette formation[44,45]. Histology is a powerful tool for diagnosis, with high specificity (81%-99%) and predictability (62%-91%) but low sensitivity (36%-57%)[45]. Some cases also demonstrate biliary duct alterations, such as inflammatory infiltration of duct cells, cholestasis and ductopenia, which might represent an overlapping syndrome[46].

Genetic and immunologic markers

Some studies have unveiled the association of AIH with genetic markers, and the impact of immunophenotyping on clinical practice has been described.

Although the pathogenesis of AIH is not fully understood, susceptibility is partly determined by the presence of genes related to major histocompatibility complex Ⅱ (MHC Ⅱ) and most directly to human leukocyte antigen (HLA)[7,47]. The main associations are with HLA-DR3 and HLA-DR4 (DRB1*03 and DRB1*04) in Europeans and North Americans[48]. In children, HLA-DRB1*1301 is related to susceptibility to HAI, determining the prognosis and response to treatment[47,49]. The findings of the immunophenotyping in HAI are shown in Table 2.

Some conclusions can be drawn from these studies, in addition to some controversial findings[48-57]. Fortes Mdel *et al*[50] showed that patients presenting the HLA-DRB1*1301 allele were associated with a higher likelihood of developing cirrhosis. Czaja *et al*[56] concluded that patients with -DRB1*03 were younger at disease onset than patients with -DRB1*04, and they also had worse responses to corticotherapy. Patients expressing HLA

Table 1 Autoantibodies studies and their findings

Type of AIH	Autoantibodies	Antigen	Meaning
AIH type 1	Anti-actin	Actin	Poor response to treatment with corticosteroids[19-21]
AIH types 1 and 2 (80%-90% of cases)	Anti-asialoglycoprotein receptor	Asialoglycoprotein receptor	Liver specific antigen and indicative of prognosis[22,23]
AIH types 1 and 2 (8%-20% of cases)	Antimitochondrial antibody-M2	Mitochondria	Favorable response to corticosteroids[24,25]
AIH type 1 (39% of cases)	Anti-chromatin	Chromatin	High titers of immunoglobulin G and shows disease activity[26,27]
AIH type 2 (32% of cases)	Anti-liver-cytosol type 1	Enzyme formiminotransferase cyclodeaminase	Diagnostic tool and marker of liver inflamation[28-30]
AIH type 1	Antibody to histone and dsDNA	dsDNA	High titers of immunoglobulin G and poor-immediate response to corticosteroids[26]
AIH type 1 (47.5% of cases)	Anti-soluble liver antigen	t-RNAs	Presence of severe forms, associated with fatal outcome[31-35]
AIH type 2 (5%-19% of cases)	LKM-3	Uridinediphosphateglucuronyl tranferase	Allows diagnosis, being sometimes the only marker identified[36]
AIH type 1	Perinuclear antinuclear neutrophil cytoplasmic antibodies	Peripheral nuclear and perinuclear antigen	Presence of severe forms; Most frequent in primary sclerosing cholagitis and primary biliary cirrhosis[36-38]

AIH: Autoimmune hepatitis; dsDNA: Double-stranded DNA.

DRB1*04 are more often women, with a greater risk of comorbidity with other immune diseases and with good responses to corticosteroids[56,58].

In contrast, MHC Ⅱ antigens have shown significant heterogeneity among different ethnicities. Patients with HLA-DRB1*13 and -DRB1*03 have an earlier onset of disease compared to other patients, possibly because their ethnic groups that have a tendency toward AIH onset at younger ages. Moreover, certain ethnic groups have low prevalences of these immunophenotypes, such as the populations of Mexico and Japan, where HLA-DRB1*04 is more common, and these low rates seem to establish increased susceptibility to the disease in older people[50-52]. Few studies have demonstrated the role of immunophenotypes in HAI in children; to apply these markers as indicators of response to treatment and prognosis, more studies are needed.

The known physiopathological mechanism in AIH consists of an inflammatory response with T-lymphocyte cells, principally helpers, and B lymphocytes, macrophages and natural killer cells. The triggering factor or factors that stimulate this inflammatory response are not yet known. Several mechanisms have been proposed that would partially explain the immunologic findings of AIH[7,59].

Studies in adults and children have identified some potential pathways for the damage observed in AIH, such as the deregulation of immunoregulatory mechanisms. Some of the studies have shown that AIH patients have reductions in the number and function of T lymphocytes $CD4^+CD25^+$, which is one of the regulatory cells (T-regs) that normally represent 5%-10% of CD4 T cells in healthy humans[7,59-66]. These cells suppress the proliferation and cytokine responses of effectors CD4 and CD8 T cells, and they down-regulate the functions of macrophages, dendritic cells, natural killer cells, and B lymphocytes[62].

All immune findings are more pronounced in the initial presentation than after remission with treatment[61,62,66,67]. T-reg immunosuppressive functioning causes the production of anti-inflammatory cytokines, such as interleukin-4 (IL-4), interleukin-10 (IL-10) and transforming growth factor (TGF)-beta[68,69]. The surface markers involved in anti-inflammatory mechanisms are glucocorticoid-induced tumor necrosis factor receptor (CD62L), cytotoxic T lymphocyte-associated protein-4 (CTLA-4) and fork head/winged helix transcription factor (FOXP3)[62,70]. If the mechanisms of failure become known, new treatments, based on recuperation of the function of T-regulation, could be used in AIH[70-72].

Natural killer T cells ($CD3^+$ and $CD56^+$) are found in reduced numbers, producing lower levels IL-4 and IL-2 in AIH patients. These lower levels result in reduction of the surface expression of CTLA-4 in $CD4^+$T cells, playing a pivotal role in liver autoaggression, especially during the active phase of the disease[61,72]. Kurokohchi *et al*[73] also found that the levels of CTLA-4 were reduced in inflammatory cells from the peripheral blood of AIH patients, compared with controls, while levels of $CD80^+$ and $CD86^+$ were increased in liver-infiltrating cells. Other research has shown that the CCR5 cytokine receptor was preferentially expressed on Th1 cells. This cytokine plays a pivotal role in the recruitment of interferon-gama (IFN-γ) (a pro-inflammatory cytokine), producing $CD4^+$ T cells at inflammatory sites, such as hepatic tissue, and promoting hepatocyte damage in AIH[73,74]. Another possibility involves the presence of CD4 and/or CD8 self-reactive T cells, which could damage liver cells. These cells are found in healthy people, but in AIH patients, they are 10-fold higher in number[68,75].

Studies have also suggested that mutations in these genes act as precursors of the surface markers of immune cells and might also have significance in autoimmune diseases because changes in HLA (MHC) are absent in some patients. Mutations of several lympho-

Table 2 Major histocompatibility complex class Ⅱ human leukocyte antigen and its association with autoimmune hepatitis patients

Ref.	Total No. of patients/ controls (No. of children)	What was evaluated	Conclusions
Donaldson *et al*[48]	96/100 (no)	HLA-DR	HLA-DR3 and DR4 genes independently confer susceptibility to autoimmune hepatitis
Fortes Mdel *et al*[50]	41/111 (13)	HLA-A, -B, -C, -DR and DQ	Regarding HLA-A and -C there were no significant differences 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 more frequent in children
Ota *et al*[51]	51/no (no)	HLA-DR and -DQ	Increased frequency of all HLA-DRB1*04 alleles, principally -DRB1*0405. Secondary association with -DRB1*15 and DRB1*16
Vázquez-García *et al*[52]	30/175 (not cited)	HLA-A, -B, -C, -DR and -DQ	A significant association with HLA-DRB1*0404 was found. It was present in patients with average age onset. DQB1*0301 had a low frequency in patients and may represent a protective factor; No association was found with any class Ⅰ antigen
Fainboim *et al*[53]	52/197 (all)	HLA-A, -B, -C, -DR and -DQ	No significant associations with HLA class Ⅰ antigens were found; HLA-DR6 group (HLA-DRB1) showed increased frequency, principally HLA-DRB1*1301; The analyses of HLA-DQ group showed an associations of HLA-DQB1*0603
Pando *et al*[54]	206/208 (122)	HLA-DR and -DQ	The frequencies of HLA-DRB1*1301, -DRB1*0301, -DQA1*0103, -DQB1*0603 were significantly increased on AIH patients; HLA-DRB1*1301 was associated with younger age at disease onset, being the allele associated with AIH in children and HLA-DRB1*1302 worked as a protective factor
Bittencourt *et al*[55]	139/129 (74)	HLA-DRB and -DQB1	In AIH type 1, there was significant increase in the HLA-DRB1*13, -DRB1*03, -DRB3 and -DQB1*06 alleles in patients. HLA-DRB1*13 was more frequent in children than adults. The low frequency of HLA-DQB1*0301 may indicate a protective role of this allele; In AIH type 2, a significant increase in DRB1*07, DRB1*03, DRB4 and DQB1*02 was observed
Czaja *et al*[56]	86/102 (not cited)	HLA-A, -B, -C, -DR and -DQ	DRB4*0103 is associated with immune diseases, DRB1*0301 with a poor treatment response, and DRB1*0401 with a lower frequency of hepatic death or transplantation
Czaja *et al*[57]	210/396 controls with other chronic liver disease/102 healthy controls (no)	HLA-DR B1*03, -DRB1*04 and -DRB1*13	The frequency of HLA DRB1*13 was higher in patients without -DRB1*03 and -DRB1*04; Primary sclerosing cholangite patients showed a similar frequency of HLA-DRB1*13 when compared with AIH patients

HLA: Human leukocyte antigen; MHC: Major histocompatibility complex; AIH: Autoimmune hepatitis.

cyte surface markers studied could represent molecular markers of autoimmunity in AIH. Among them is the CTLA-4 (CD152) gene mutation, which has appeared in controversial reports of the phenotypes that represent susceptibility to AIH[76-81]. For instance, in the Brazilian study by Bittencourt *et al*[77] no association was established between exon 1 *CTLA-4* gene polymorphisms at position 49 and AIH susceptibility, contradicting findings in a North American population[78].

CTLA-4, which is expressed on the surface of T cells, induces peripheral tolerance by biding CD80 and CD86 on antigen-presenting cells. In doing so, CTLA-4 competes with the co-stimulatory molecule CD28, reducing the immune response[47]. CTLA-4 is considered a critical coordinator in immune regulation. Based on this finding, some researchers have attempted to find a drug that simulates its mechanism and that could be used in the treatment of autoimmune conditions; one such drug is an immunoglobulin G-CTLA-4 (Abatacept), which was recently approved by the FDA for use in rheumatoid arthritis[82,83].

Furthermore, some studies have aimed to evaluate whether a *Fas* gene polymorphism or its increased expression on lymphocyte surfaces could be key mechanisms for autoimmunity in AIH. Fas (CD95) is part of the tumor necrosis factor family, and it induces receptor-mediated programmed cell death (apoptosis) through engagement with its ligand (FasL/CD95L). It indirectly controls the number of antigen-activated lymphocytes[84]. Ogawa *et al*[85] showed that AIH patients show an increase in CD95 (Fas)-positive $CD4^+$ and $CD8^+$ T cell numbers. These individuals show disease courses with high levels of conversion of naive $CD45RO^-$ to primed $CD45RO^+$ $CD4^+$ T cells. This course could indicate that constant activation of T lymphocytes and/or the persistent presence of activated lymphocytes requires continuous work from regulation cells, such as $CD95^+$ T $CD4^+$[85]. Tsikrikoni *et al*[86] also found a greater number of Fas^+ and $FasL^+$ cells in the mononuclear cells of AIH patients and increased TNF-α and IFN-γ production in cultured cells, suggesting that these cytokines could be involved in accelerating apoptosis. They also showed an increase in $CD14^+$ monocyte cell numbers, in accordance with the increased

expression of apoptotic markers, such as $CD14^+$ cells, responding to the clearance of apoptotic cells[87]. Concomitantly, the results of genetic studies have shown that some mutations can affect the function of Fas receptors, but more research is needed to determine these receptors' relationship with AIH[88-91].

A lack of consistent evidence has persisted for studies evolving genes of cytokines, such as tumor necrosis factor; TGF-beta1, and TBX21, (a regulator of T lymphocyte lineage development and a controller of the expression of IFN-γ)[91-98].

TREATMENT

An important feature of AIH is response to treatment with corticosteroids and immunosuppressants[2,6,99]. Prednisone alone or in combination with azathioprine is the main form of treatment[99]. This treatment has the goal of reducing hepatic inflammation, the induction of clinical remission, relief of symptoms and improvement of survival. The treatment response characterizes clinical improvement and a reduction of aminotransferases to normal or to no more them two times of the maximum of the reference value, while remission lies in clinical improvement, normalization of aminotransferases and gamma globulin, autoantibody reduction or extremely low titers of autoantibodies and histological resolution of inflammation with a reduction in fibrosis[3,44]. Moreover, relapse is characterized by increased transaminases after remission has been achieved, as shown by Ferreira *et al*[44,100]. Relapse is common during treatment and occurs in up to 40% of patients, requiring a temporary increase in the dose of corticosteroid[3,99]. Noncompliance play a prominent role in a percentage of relapses[44,100]. Some medications offer alternative treatment, such as cyclosporine, tacrolimus and mycophenolate mofetil. These drugs are reserved for patients who fail to respond to the first treatment choice[2,6]. In cases of autoimmune sclerosing cholangitis and autoimmune cholangitis, the use of ursodeoxycholic acid can be necessary to control bile duct disease[2].

Liver transplantation is the last-line treatment indicated for patients who have not responded to medication. The need for transplantation is present in 8.5% of children with HAI[8]. The total duration of immunosuppressive therapy has not been established, but in the face of the possible side effects with medication, discontinuation of treatment should be considered when the remission criteria are met in patients with type 1 AIH[3]. To meet this goal, the patient must present histological resolution of inflammation after at least two years of clinical and laboratory remission (normal liver enzymes, liver function and gamma globulin and autoantibodies in low or undetectable titers)[3]. Approximately 20% of patients with type 1 AIH can remain in remission after discontinuation of treatment, but relapses are frequent after the suspension of treatment[6,8,100]. In type 2 AIH, treatment discontinuation is not recommended because relapses are more frequent, and failure of remission upon suspension is almost certain in this condition[8].

The prognosis of patients who respond to immunosuppressive treatment is good, even when there is cirrhosis at baseline; there is a good quality of life and, in general, use of low doses of medication[2-4]. Except for the changed autoantibodies that were initially detected, no markers are currently used in clinical practice to choose and follow treatment.

CONCLUSION

In conclusion, recent studies have shown new possibilities for the diagnosis and prognostic evaluation of AIH, except for in the pediatric age group, which remains unrepresented in these assessments. Susceptibility to autoimmune diseases is multifactorial, but genetic and immunological factors play pivotal roles. MHC Ⅱ antigens could represent a susceptibility marker for AIH, considering the differences between ethnic groups, or they might predict treatment response and prognosis. Finally, in pediatric populations, the prevalence and titers of autoantibodies can be different from in adults, such as for the MHC Ⅱ HLA-DRB1*1301, which can be a marker of susceptibility in the pediatric population.

Perhaps in the future, knowledge of autoimmune mechanisms will reveal better markers for the diagnosis, monitoring and treatment of AIH and other autoimmune diseases, but there are still only few available studies with good suggestions for markers.

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