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Review Article

Autoimmune Liver Disease in Children

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Abstract

Autoimmune liver disease in children encompasses autoimmune hepatitis (AIH), AIH overlapping with sclerosing cholangitis, drug induced AIH, AIH in syndromes, systemic disease and AIH after liver transplantation (LT). AIH is an uncommon progressive disease of the liver of unknown etiology affecting all ethnic groups and with female predilection. Characteristic clinical findings include elevated transaminases, elevated total Immunoglobulin G, positive autoantibodies and interface hepatitis on liver histology, in the absence of other known causes of liver disease. A scoring system is available to enable diagnosis given there is no single pathognomonic feature for AIH. AIH is designated as type 1 when there is positivity for antinuclear antibody +/- smooth muscle antibody and type 2 when there is positivity for liver kidney microsomal antibody demonstrated. Clinical presentation can range from asymptomatic to acute hepatitis like picture, jaundice, acute liver failure, and end-stage liver disease. AIH is characteristically treated with immunosuppression. Patients who have overlap with sclerosing cholangitis respond biochemically to ursodeoxycholic acid (UDCA), but effect on long-term outcome in children is unclear. LT is indicated in acute liver failure with encephalopathy or end-stage liver disease. AIH may recur after LT and also may occur denovo in a proportion of children transplanted for conditions other than AIH.

ABBREVIATIONS

AIH: Autoimmune Hepatitis; SC: Sclerosing Cholangitis; LT: Liver Transplantation; IgG: Immunoglobulin G; ANA: Antinuclear Antibody; SMA: Smooth Muscle Antibody; LC1: Liver Cytosolic antigen type1; APECED: Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy; AIRE: Autoimmune Regulator; IBD: Inflammatory Bowel Disease; ANCA:

Antineutrophil Cytoplasmic Antibody; SLA: Soluble Liver Antigen; AZA: Azathioprine; TPMT: Thiopurine Methyl Transferase; 6-TG 6- Thioguanine; 6MMP 6-methylmercaptopurine; MMF: Mycophenolate Mofetil; UDCA: Ursodeoxycholic Acid, HSV: Herpes Simplex Virus; LKH: Liver-Kidney Microsomes

INTRODUCTION

Autoimmune liver disease in children encompasses

autoimmune hepatitis (AIH), AIH overlapping with sclerosing cholangitis (SC), drug induced AIH, AIH in syndromes, systemic disease and AIH after liver transplantation (LT) both recurrence of AIH and development of 'de novo' AIH. This review will focus mainly on AIH and briefly describe the other entities. Autoimmune hepatitis (AIH) is a rare progressive inflammatory disorder of unknown etiology. It is characterized biochemically by elevated transaminases and serum immunoglobulin G (IgG), serologically by the presence of non-organ specific and liver specific autoantibodies and histologically by interface hepatitis. The diagnosis is made after other known causes of liver disease have been excluded and typically there is response to immune suppression. The type of autoantibody detected in the serum allows 2 types of AIH to be characterized. In type 1 AIH there is positivity for antinuclear antibody (ANA) and/or smooth muscle antibody (SMA) while in type 2 there is positivity for liver kidney microsomal antibody (anti-LKM) or antibody to liver cytosolic antigen type 1 (LC1). AIH is primarily a pediatric disease with 40% of type 1 AIH and 80% of type 2 diagnosed before 18 years of age. AIH is seen in all ethnic groups and the prevalence varies geographically. The reported prevalence ranges from 1.9 cases per 100,000 in Norway and 1 per 200,000 in the US general population to 20 per 100,000 in females over 14 years of age in Spain [1,2].

AIH was previously referred to as 'chronic active hepatitis' and was first described by Waldenström in 1950, when he drew attention to its predominance in young women with fluctuating course, extreme hypergammaglobulinemia, associated features of arthralgia/myalgia, hepatosplenomegaly, amenorrhea, skin rashes and invariably fatal outcome [3]. The 'autoimmune' basis of this condition was widely accepted only after the controlled trials of the early 1970's demonstrated response to immunosuppressive therapy [4, 5] and a link with HLA antigens B8, DR3 was established [6] similar to other disorders that were autoimmune in origin. After the identification of hepatitis C in 1989, there was considerable anxiety about the fact that chronic hepatitis C and other viral hepatitis were wrongly being assigned a diagnosis of AIH. A panel of experts (International Autoimmune Hepatitis Group IAHG) was convened to establish criteria for making a diagnosis of AIH [7].

PATHOGENESIS

The pathogenic mechanisms leading to the development of AIH in particular and autoimmunity in general remain unknown. Both cellular and humoral mechanisms appear to be involved. It has been hypothesized that a genetically predisposed host is exposed to an environmental agent, which triggers an autoimmune process directed at liver antigens, causing a progressive necroinflammatory process resulting in fibrosis and cirrhosis [8]. High amounts of interferon (IFN)- γ producing CD4 T cells and CD8 T cells are associated with biochemical evidence of liver damage in AIH, suggesting a combined cellular attack. It is hypothesized that an auto antigenic peptide in association with a HLA class II molecule is presented by antigen presenting cells to naïve CD4 T-helper (Th0) cells [1]. There is differentiation into T-helper type 1 cells if there is predominance of interleukin-12 and T-helper type 2 cells if interleukin-4 is predominant in the microenvironment. This then leads to release of inflammatory

cytokines including IFN- γ , activation of CD8 T cells and antibody production by B lymphocytes. The process of auto antigen recognition is controlled by regulatory mechanisms including CD4+CD25+ regulatory T cells which are produced when the milieu is rich in TGF-beta. If regulatory mechanisms fail, then an autoimmune attack is perpetuated [1].

It has been postulated that HLA B8 is a marker of abnormal T cell function and that individuals with this antigen are unable to switch off immune and autoimmune reactions triggered by environmental factors [9]. The ability of auto reactive T cells to proliferate is controlled by the regulatory T-cell (Treg) subset that is characterized based on surface expression of CD4 and CD25 and nuclear expression of the fork head transcription factor box P3 [2]. Reduced quantity and function of Tregs have been demonstrated in AIH and functional deficiencies of Tregs have been shown to inhibit T-cell proliferation and gamma-IFN production resulting in hepatocyte injury [10, 11]. The HLA A1 B8 DR3 haplotype is characteristically associated with AIH and other autoimmune conditions including autoimmune thyroiditis, systemic lupus erythematosus, insulin dependent diabetes mellitus in which there is increased production of antibodies to exogenous and endogenous antigens [12]. Despite this genetic susceptibility, there is lack of concordance in identical twin pairs in most autoimmune diseases. There is a report in which the only difference in HLA identical twins was exposure to HSV in the twin who had AIH [13]. That structural similarity between virus and host, a phenomenon called 'molecular mimicry' may be the mechanism triggering autoimmunity was suggested in the early 80's [14]. Cytochrome P4502D6 (CYP2D6) is the main target autoantigen in AIH type 2, where the serological marker is liver kidney microsomal antibody [15]. There is sequence homology between CYP2D6 and hepatitis C virus [15], CYP2D6 and other viral proteins including cytomegalovirus, Epstein-Barr virus and herpes simplex virus. This homology has led to the hypothesis that a viral antigen may be the trigger for the production of antibody in AIH type 2 [16]. The other mechanism linking autoimmunity to infections is indirect - i.e. bystander activation and super-antigen mediated activation of auto-reactive T and B cells. It has been reported that hepatitis A, B and C can also trigger AIH [17-19].

A CYP2D6 mouse model has been developed on this concept of molecular mimicry rather than identity and has been successful in establishing a model for chronic liver damage and reflects many features of human AIH [20]. The liver damage is longstanding, in contrast to animal models described in the past which were based on repeated immunization with heterologous (human) liver antigen preparation in complete Freund's adjuvant [21] where the liver damage was transient. These early studies however helped to identify liver specific protein as a putative auto antigen in autoimmune liver disease and later led to the identification of antibodies to asialoglyco protein receptor [22] and soluble liver antigen [23]. Single gene defects may also cause AIH, such as in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome that affects the generation of an autoimmune regulator (AIRE) protein [24].

CLINICAL FEATURES & DIAGNOSIS

Presentation in AIH is primarily in pediatric age group, with female preponderance. Peak incidence is in the pre-

pubertal age, although infants have been diagnosed with AIH. The majority of children present usually during adolescence with ANA/SMA positivity and a smaller proportion present at a younger age with LKM antibody positivity. There is usually a family history of autoimmune disease. The mode of presentation is variable and includes (i) acute viral hepatitis like picture with malaise, abdominal pain followed by jaundice (ii) insidious onset with fatigue, weight loss, relapsing jaundice (iii) asymptomatic – picked up on screening (iv) acute liver failure and (v) complications related to portal hypertension like gastrointestinal bleeding, splenomegaly and ascites. Physical examination is variable depending on severity of disease. There may be a palpable liver, spleen or both. Unlike adults, clubbing, palmar erythema and spider nevi are uncommon in childhood. Laboratory tests may show evidence of hypersplenism with low white cell and platelet count; elevated transaminases, high total protein with low albumin, high immunoglobulin G and presence of antinuclear antibody, smooth muscle antibody, and or liver kidney microsomal antibody. Other antibodies seen in AIH include LC1, soluble liver antigen [23], and peri-nuclear staining anti neutrophil cytoplasmic antibody (p-ANCA), the latter is seen usually when there is associated SC. There may be prolonged prothrombin time and elevated ammonia in an acute liver failure setting. Some patients may present with jaundice. Ultrasound may demonstrate a heterogenous liver and occasionally ascites.

The histology in AIH is characteristic and essential in making a diagnosis of AIH. The term 'interface hepatitis' has replaced the term 'piece-meal necrosis'. The liver biopsy typically demonstrates a predominantly lymphoplasmacytic necroinflammatory infiltrate with or without lobular (intra-acinar) involvement, portal-portal and central-portal bridging necrosis, often with the formation of liver cell rosettes and nodular regeneration (Figure 1) [25]. This histological picture is not exclusive to AIH and may be seen in viral hepatitis. Histological evidence of cirrhosis can be found in up to 50% of biopsies of pediatric patients with AIH at presentation (Figure 2a

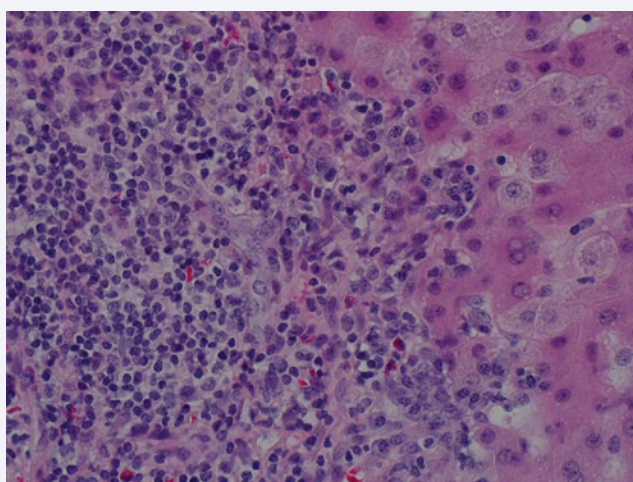


Figure 1 Autoimmune hepatitis. A heavy inflammatory infiltrate is present in the portal tract. The majority of the inflammatory cells are plasma cells (blue arrows). There is prominent interface hepatitis (black arrow). Magnification at 400X. H&E (Photomicrograph courtesy of Dr. Nick Shillingford, Children's Hospital Los Angeles).

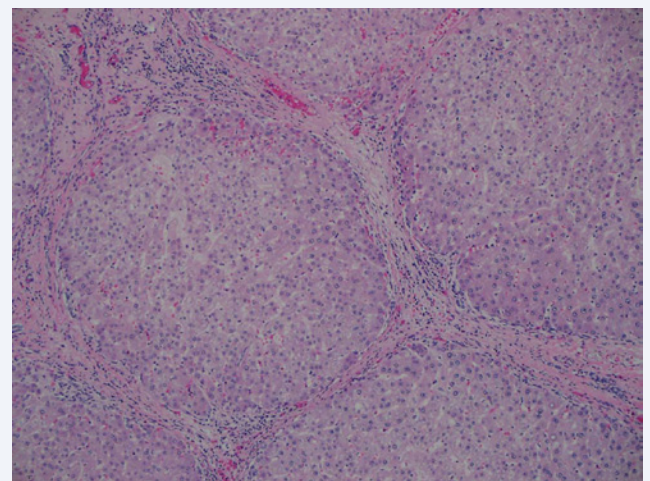


Figure 2a Cirrhotic liver in a patient with autoimmune hepatitis. The liver parenchyma is divided into lobules by fibrous septa. The nodules are well demarcated. There is a brisk inflammatory infiltrate with a predominance of plasma cells. Interface activity is mild. Magnification at 100X. H&E. (Photomicrograph courtesy of Dr. Nick Shillingford, Children's Hospital Los Angeles).

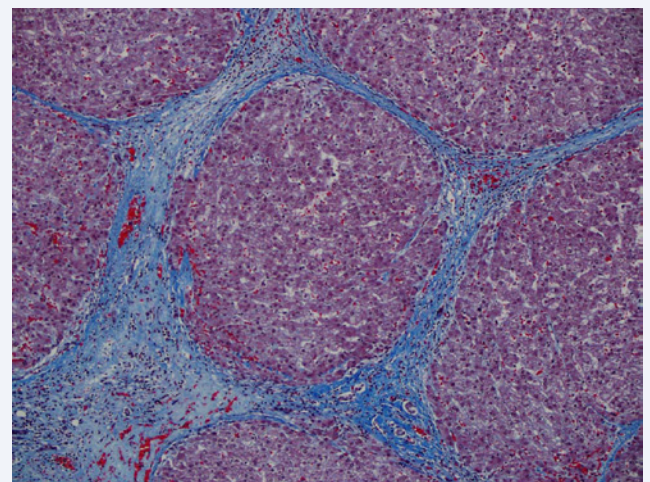


Figure 2b Cirrhotic liver in a patient with autoimmune hepatitis. Parenchymal nodules are separated by fibrous septa. Magnification at 1000X. Masson trichrome stain. (Photomicrograph courtesy of Dr. Nick Shillingford, Children's Hospital Los Angeles).

and b) [26]. Occasionally, classical features of AIH may be seen histologically in the absence of autoantibodies. This is referred to as 'seronegative AIH' and 7/72 children with AIH who were seronegative were treated successfully with immunosuppression [27]. Autoantibodies may also be absent in an acute liver failure setting.

Autoimmune liver disease may be associated with other autoimmune disorders including thyroiditis, inflammatory bowel disease, vitiligo, insulin dependent diabetes mellitus and nephrotic syndrome [28]. Systemic lupus erythematosus is also associated with AIH, although there may be other causes of liver abnormalities in these patients [29]. The APECED syndrome caused by mutation of AIRE protein is associated

with AIH in up to 20% of cases and has an autosomal recessive inheritance. Another syndrome associated with AIH is IPEX (Immune dysfunction, Polyendocrinopathy, Enteropathy, X-linked) immunodysregulation, with low IgG, high IgM and CD40 ligand deficiency [30]. Patients with AIH may have a genetically determined deficiency of complement C4 and partial IgA deficiency.

SC is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the biliary system, leading to biliary cirrhosis and sometimes cholangiocarcinoma. Although the condition was first described in 1924, recognition was rare as it was found at laparotomy in cholestatic patients. In the 90's when cholangiography both endoscopically and radiologically became widely available, diagnosis of SC became more frequent. Primary SC (PSC) has a male predilection and is associated with inflammatory bowel disease (IBD). Up to 81% of children with PSC have or will develop IBD [31]. Subjects with SC are identified on the basis of abnormal liver function tests, in particular elevated levels of alkaline phosphatase or gamma-glutamyltransferase (GGT). These patients may also have increased levels of IgG and IgM and positive autoantibodies (ANA, SMA, ANCA). ANCA are a fairly consistent feature of PSC. ANCA associated with PSC and AIH type 1 are distinct from cytoplasmic ANCA and classical perinuclear ANCA, which are diagnostic seromarkers for Wegener's granulomatosis and microscopic polyarteritis, respectively. PSC, ulcerative colitis, and AIH are associated with "atypical perinuclear ANCA," which has a distinct staining pattern on indirect immunofluorescence microscopy [32]. Children who have positive autoimmune serologies with interface hepatitis and biliary changes on biopsy and/or radiological changes consistent with SC are described to have an overlap syndrome of AIH and PSC – autoimmune SC [33]. Surveillance for SC in children with AIH, particularly when the GGT is high allows diagnosis early.

Celiac disease may be found in association with other autoimmune disease. In an Italian study, 6.4% of 47 AIH patients were positive for IgA anti-tissue transglutaminase antibody and celiac disease was confirmed after small bowel biopsy [34]. In another study of 350 children with celiac disease, 140 had elevated transaminases – 133 had cryptogenic disease, and 7 AIH. The transaminases normalized after gluten free diet in those with cryptogenic disease and with additional immunosuppressant therapy in AIH [35]. Drug induced AIH- has been reported. A recent study demonstrated that 9.2% of 261 adult patients had AIH secondary to drugs [36]. The two most commonly identified drugs were nitrofurantoin and minocycline and while clinical and histological patterns were similar to AIH not induced by drugs, the patients with drug-induced AIH did not appear to require long-term immunosuppressive therapy.

SCORING SYSTEM

The diagnosis of AIH can be challenging with no single pathognomonic feature. Mortality is high without early diagnosis and treatment. The International Autoimmune Hepatitis Group (IAHG) developed and subsequently revised a scoring system to weigh each clinical, laboratory and histological finding at presentation as well as after corticosteroid therapy [25]. A pretreatment score of 15 and post treatment score of 17 was considered indicative of 'definite' AIH, with a sensitivity of 95%,

a specificity of 97% and a diagnostic accuracy of 94% [24]. The scoring system was originally designed for scientific purposes and found to be too complicated for routine clinical use. The scoring system has since been further simplified using reduced number of parameters: Autoantibody (ANA, SMA, LKM or SLA) positivity, elevated IgG, characteristic liver histology and absence of viral hepatitis [37].

MANAGEMENT

The goal of management is to control liver inflammation and prevent progress to cirrhosis. Immunosuppression has been the mainstay of therapy. Adherence to medical management is paramount for successfully managing AIH and it is advisable to use objective measures rather than relying solely on subjective measures [38]. Conventional treatment in AIH consists of steroids with or without an added agent, typically Azathioprine (AZA). Prednisone is usually started at a dose of 2 mg/kg/day, maximum dose 40-60 mg. This is gradually tapered by 5 mg weekly after the transaminases have significantly reduced. The timing of the addition of a steroid sparing agent, AZA is variable, but it is reported that up to 85% of patients have eventually required it [39]. Some wait till the patient develops significant side-effects on the dose of steroids required to maintain remission, or is unable to achieve remission on steroids alone before adding AZA, while others add it at diagnosis. It is advised to exercise caution, as AZA can be hepatotoxic, particularly if presentation is with severe cholestasis and/or acute liver failure. It is helpful to measure thiopurine methyl transferase (TPMT) enzyme activity before starting AZA, so that the dose of the drug can be adjusted appropriately and toxicity avoided [40]. Side effects of AZA include leukopenia, pancreatitis and hepatotoxicity. The drug is usually started at a dose of 0.5 – 2 mg/kg per day. The dose may be titrated based on levels of the AZA metabolites - 6-thioguanine (6-TG, active metabolite) and 6-methylmercaptopurine (6-MMP, hepatotoxic metabolite) [41]. If the 6-TG levels are low, then the dose of AZA is increased and if the 6-MMP levels are high, then it is reduced. Occasionally, the 6-TG is low, but the 6-MMP is paradoxically elevated, in this situation, one can add allopurinol to divert the metabolism to the 6-TG pathway [42]. Measuring the levels of the metabolites also allows monitoring of adherence and is similar to measuring HbA1C in a diabetic patient as it gives an idea of disease control over a period of time. Other drugs that have been used in the control of AIH include Mycophenolate Mofetil (MMF), cyclosporine and tacrolimus [43]. MMF is the prodrug of mycophenolic acid and arrests DNA replication in T and B lymphocytes by inhibiting de novo purine synthesis. MMF is given at a dose of 20-30 mg/kg/day in 2 divided doses. Side effects include gastrointestinal symptoms (nausea, diarrhea), headaches, hair loss and bone-marrow suppression. In a series of 26 children with AIH, 18 responded to MMF and the authors concluded that MMF is an effective rescue therapy in AIH, but not for those with disease overlapping with sclerosing cholangitis [32]. Ursodeoxycholic acid is added when there is overlap with SC.

Budesonide has been reported to have an advantage over conventional steroids like Prednisone as it has a high first pass clearance by the liver, low systemic availability and metabolites that lack glucocorticoid activity [44]. In a large multicenter

double blind controlled study, 203 adults with non-cirrhotic AIH were given AZA (1-2 mg/kg/day) with either budesonide (3mg, three times daily or twice daily) or prednisone (40 mg/day, tapered to 10mg/day); 47% in the budesonide group versus 18.4% in the prednisone group achieved completed biochemical remission without predefined steroid side-effects[44]. While Budesonide worked well in reducing steroid associated side-effects, it is important to give the drug in combination with AZA to induce remission.

Long-term immunosuppression is required in the majority of children with AIH. Maintenance therapy is typically with AZA or MMF, prednisone being reserved for treatment of relapse. Measurement of autoantibody titers and IgG levels are useful in assessing disease activity in addition to standard liver function tests given repeated liver biopsies are not feasible. It is advisable not to attempt to withdraw treatment within 3 years of diagnosis or during/immediately before puberty, when relapses are common. Some routinely perform liver biopsy to assess histological remission before stopping immunosuppression. In type 2-AIH it is usually not possible to discontinue drugs.

Assessing adherence to the medication regimen is extremely important. It is important to use objective measures like drug levels or electronic monitoring [38] to assess adherence rather than subjective measures like questionnaires for patient or caregiver. AIH is most prevalent in adolescents and this age group is the most likely to be non-adherent. Medication changes are recommended only after it has been established that the patient is not achieving remission on the prescribed regimen.

LIVER TRANSPLANTATION, RECURRENT AND 'DE NOVO' AIH

Therapy with immunosuppression in AIH requires lot of caution in an acute failure setting as there is a significant risk of developing infections and this can become a contraindication for liver transplantation (LT) [45]. Liver transplantation is indicated when a child with AIH presents with acute liver failure and encephalopathy. Development of end-stage liver disease despite medical therapy is also an indication for LT and 15.4% of 65 children diagnosed with AIH received liver transplants over a 20 year period [46]. Children transplanted for AIH receive added immunosuppression after LT to reduce risk of relapse. Recurrence of AIH after transplantation has been reported in up to 20% of patients [47]. Recurrence is managed with increasing immunosuppression and adding a third agent like AZA, MMF or rapamycin [48]. 'De novo' AIH is seen in 6-10% of children transplanted for non-autoimmune disorders. This form of graft dysfunction is characterized by the presence of autoantibodies, elevated IgG, histological features of AIH and responds to treatment with steroids and AZA as in classical AIH, with reduction in calcineurin inhibitor dose [49].

DISCUSSION AND CONCLUSION

AIH is a progressive inflammatory disease of the liver, diagnosed histologically in the absence of other liver disease. Type1 AIH is characterized by the presence of ANA +/- SMA and type 2 AIH by LKM antibody. The etiology of AIH is not known but thought to be multi-factorial. Clinical presentation can range

from insidious onset to acute liver failure. Association with other autoimmune disorders and family history of autoimmune disease is common. There is no pathognomonic feature of AIH although interface hepatitis is characteristic on liver biopsy and a scoring system is in place for diagnosis. AIH responds to immunosuppression in the majority of cases, steroids and azathioprine being most commonly used. Mycophenolate Mofetil, calcineurin inhibitors and rapamycin have been used in refractory cases. Liver transplantation is indicated in a minority when there is acute liver failure with encephalopathy and in end-stage liver disease. AIH may recur after LT and 'de novo' AIH should be ruled out when there is graft dysfunction. In the vast majority, AIH has a good prognosis on medical treatment with immunosuppression and a proportion can be successfully weaned off therapy.

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