

Autoimmune Liver Disease in Children

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Abstract

Autoimmune liver disorders are characterised by an inflammatory liver histology, circulating non-organ specific autoantibodies and increased levels of immunoglobulin G (IgG) in the absence of a known aetiology. They respond to immunosuppressive treatment, which should be instituted as soon as diagnosis is made. Liver disorders with a likely autoimmune pathogenesis include autoimmune hepatitis (AIH) and autoimmune sclerosing cholangitis (ASC). Two types of AIH are recognised according to seropositivity for smooth muscle and/or antinuclear antibody (SMA/ANA, type 1) or liver kidney microsomal antibody (LKM1, type 2). There is a female predominance in both. LKM1-positive patients tend to present more acutely, at a younger age, and commonly have immunoglobulin A (IgA) deficiency, while duration of symptoms before diagnosis, clinical signs, family history of autoimmunity, presence of associated autoimmune disorders, response to treatment and long-term prognosis are similar in both groups. The most common type of paediatric sclerosing cholangitis is ASC. The clinical, biochemical, immunological and histological presentation of ASC is often indistinguishable from that of AIH. In both, there are high IgG, non-organ specific autoantibodies and interface hepatitis. Diagnosis is made by cholangiography. Children with ASC respond to immunosuppression satisfactorily and similarly to AIH in respect to remission and relapse rates, times to normalisation of biochemical parameters and decreased inflammatory activity on follow-up liver biopsies. However, the cholangiopathy can progress and there may be an evolution from AIH to ASC over the years, despite treatment. Whether the juvenile autoimmune form of sclerosing cholangitis and AIH are 2 distinct entities, or different aspects of the same condition, remains to be elucidated.

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Introduction

Autoimmune liver disorders are inflammatory liver diseases characterised histologically by a dense mononuclear cell infiltrate, including plasma cells, in the portal tract (Fig. 1) and serologically by the presence of non-organ and liver-specific autoantibodies and increased levels of immunoglobulin G (IgG), in the absence of a known aetiology. They usually respond to immunosuppressive treatment, which should be instituted as soon as diagnosis is made. The onset of these conditions is often ill-defined, frequently mimicking acute hepatitis.^{1,2} There are 2 liver disorders in which liver damage is likely to arise from an autoimmune attack: autoimmune hepatitis (AIH) and autoimmune sclerosing cholangitis (ASC).

Autoimmune Hepatitis

Clinical Features

Two types of AIH are recognised according to the presence of smooth muscle and/or antinuclear antibody (SMA/ANA, type 1 AIH) or liver kidney microsomal

antibody type 1 (LKM1, type 2 AIH). Paediatric series,^{3,4} including our own,⁴ report a similarly severe disease in ANA/SMA-positive and LKM1-positive patients. In our retrospective review of 52 children with AIH seen between 1973 and 1993, 32 had ANA and/or SMA, and 20 had LKM1.⁴ All other known causes of liver disease were excluded. There was a predominance of girls (75%) in both groups. While LKM1-positive patients presented at a younger age (median, 7.4 years versus 10.5 years), duration of symptoms before diagnosis and frequency of hepatosplenomegaly were similar in the 2 groups. There was also no significant difference in frequency of associated autoimmune disorders and family history of autoimmune disease between the 2 groups.

We observed 3 clinical patterns of disease:

Pattern 1: In 50% of ANA/SMA-positive and 65% of LKM1-positive patients, the presentation was indistinguishable from that of acute viral hepatitis (non-specific symptoms of malaise, nausea/vomiting, anorexia and abdominal pain, followed by jaundice, dark urine and pale

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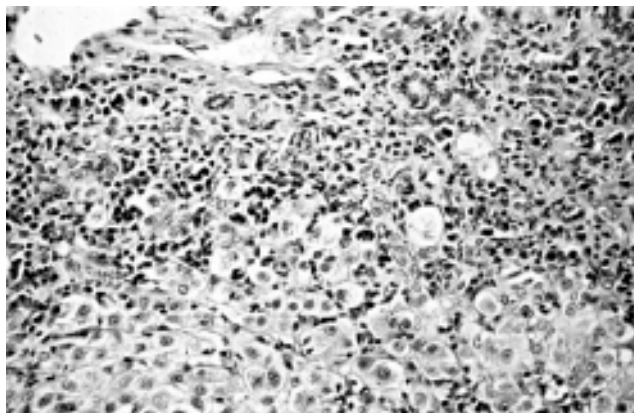


Fig. 1. Interface hepatitis characterised by a dense portal tract mononuclear cell infiltrate, including lymphocytes and plasma cells, that erodes the limiting plate and invades the parenchyma.

stools); 6 (5 were LKM1-positive) children developed acute hepatic failure with grade II-IV hepatic encephalopathy from 2 weeks to 2 months (median, 1 month) after onset of symptoms. In the remaining children the duration of disease before diagnosis ranged from 10 days to 5 months (median, 1.8 months).

Pattern 2: Twenty-five per cent LKM1-positive and 38% ANA/SMA-positive patients had an insidious onset with an illness characterised by progressive fatigue, relapsing jaundice, headache, anorexia and weight loss, lasting from 6 months to 2 years (median, 9 months) before diagnosis.

Pattern 3: In 6 (2 were LKM1-positive) patients, there was no history of jaundice and the diagnosis followed presentation with complications of portal hypertension, such as hematemesis from oesophageal varices, bleeding diathesis, chronic diarrhoea, weight loss and vomiting. The mode of presentation of AIH in childhood is therefore variable, and the disease should be suspected and excluded in all children presenting with symptoms and signs of prolonged, or severe, liver disease.

Overall, LKM1-positive patients had higher median levels of bilirubin and aspartate aminotransferase (AST) than those who are ANA/SMA-positive, but if the 6 patients presenting with acute hepatic failure are excluded, the differences for these 2 parameters are not significant. A severely impaired hepatic synthetic function, as assessed by the presence of both a prolonged prothrombin time and hypoalbuminaemia, tended to be more common in ANA/SMA-positive (53%) than in LKM1-positive patients (30%). The majority (80%) of the patients had increased levels of IgG, but 10 (5 LKM1-positive) had a normal serum IgG level for age, including 3 patients who presented with acute hepatic failure, indicating that normal IgG values do not exclude the diagnosis of AIH. As previously reported,⁵ we

found that partial immunoglobulin A (IgA) deficiency is more common in LKM1-positive than ANA/SMA-positive patients (45% versus 9%).

When compared to controls, the frequency of human leukocyte antigens (HLA) DR3 was significantly higher in patients with ANA/SMA-positive, but not with LKM1-positive AIH. Although this observation should be confirmed in a larger number of LKM1-positive patients, it suggests that the immunopathogenic mechanisms involved in the development of the 2 forms of AIH may be different.

The severity of portal tract inflammation, lobular activity and periportal necrosis at diagnosis was similar in both groups. Cirrhosis on initial biopsy was more frequent in ANA/SMA-positive (69%) than in LKM1-positive patients (38%). Of note is that 57% of patients, already cirrhotic at diagnosis, presented with a clinical picture reminiscent of that of prolonged acute viral-like hepatitis. Progression to cirrhosis was noted in 4 of 7 ANA/SMA-positive and 2 of 5 LKM1-positive patients on follow-up biopsies done between 17 to 56 months from the initial biopsy. Overall, 74% of ANA/SMA-positive and 44% of LKM1-positive patients showed evidence of cirrhosis on initial or follow-up histological assessment, indicating that apart from the higher tendency to present as acute liver failure, the severity of LKM1-positive disease is not worse than ANA/SMA-positive disease.

Treatment

Autoimmune hepatitis responds well to immunosuppression unless it presents as acute liver failure. In the latter circumstance, urgent liver transplantation is usually required. Prednisolone, 2 mg/kg/day (maximum dose, 60 mg/day), is the typical initial treatment. The dose is gradually decreased over a period of 2 to 8 weeks if there is a progressive improvement in the serum aminotransferase level. The patient is then maintained on the minimal dose of prednisolone necessary to keep the serum aminotransferase level normal (usual maintenance dose, 2.5 to 5 mg/day, depending on age). During the first 6 to 8 weeks of treatment, liver function tests are checked weekly to allow for a constant and frequent fine-tuning of the treatment and to avoid severe steroid side-effects. If a progressive normalisation of the liver function tests is not obtained over this period of time, or if too high a dose of prednisolone is required to maintain normal transaminases, azathioprine is added at a starting dose of 0.5 mg/kg/day which, in the absence of signs of toxicity, is increased up to a maximum of 2 mg/kg/day until biochemical control is achieved. Azathioprine is not recommended as first-line treatment because of its hepatotoxicity, particularly in severely jaundiced patients. In most children, an 80% decrease in the initial serum aminotransferase abnormality is achieved

within 6 weeks. Complete resolution of the liver test abnormality, however, may take several months. In our own series, normalisation of the serum aminotransferase level occurred at a median of 0.5 years (range, 0.2 to 7 years) in children with ANA/SMA and 0.8 years (range, 0.02 to 3.2 years) in children with LKM1. Relapse while on treatment is common, affecting about 40% of patients and requiring a temporary increase in the steroid dose. The risk of relapse is higher if steroids are administered on an alternate day schedule, often instituted in the belief that it has less negative effect on the child's growth. Small daily doses are preferable, since they are more effective in maintaining disease control, minimising the need for high-dose steroid pulses during relapses, with attendant more severe side effects. Discontinuation of treatment should be considered after 1 year of normal liver function tests and demonstration of minimal or no inflammatory changes in liver biopsy tissue. Treatment should not be weaned just before or during puberty since relapse is more common during this period. In our experience, treatment was successfully withdrawn in 6 of 13 children who fulfilled these remission criteria. All 6 patients had ANA/SMA. Treatment withdrawal was accomplished after a median treatment duration of 3.2 years (range, 1 to 11 years), and remission was sustained in all 6 for 9 to 13 years. The remaining 7 children relapsed between 1 and 15 months after drug withdrawal (median interval, 2 months). Three of these patients had ANA/SMA, and 4 had LKM1. All responded to re-introduction of the original treatment schedule. These observations indicate that most children with AIH, particularly those with LKM1, require life-long immuno-suppressive therapy.

Despite the efficacy of current treatment, severe hepatic decompensation may develop even after many years of apparent good biochemical control. Thus, 4 of our patients, who responded satisfactorily to immuno-suppression, ultimately required transplantation 8 to 14 years after diagnosis. Overall, in our series, 46 of the 47 patients treated with immunosuppression were alive between 0.3 and 19 years (median, 5 years) after diagnosis, including 5 after liver transplant.

Sustained remission of AIH has been reported in adult patients maintained on azathioprine alone.⁶ Following this observation, we have attempted to stop prednisolone, while maintaining azathioprine in 5 children (2 ANA/SMA-positive and 3 LKM1-positive). While the attempt was successful in ANA/SMA-positive cases, all LKM1-positive children relapsed and required reinstatement of steroid treatment.

Remission has been reported in 25 of 32 children with AIH treated with only cyclosporin A for 6 months, followed by combined low-dose prednisolone and azathioprine for

1 month, after which cyclosporin was stopped and the other 2 drugs continued.⁷ The side-effects associated with short-term cyclosporin treatment were mild, despite relatively high blood concentrations of the drug, and corticosteroid-induced side effects were avoided. A disadvantage of this schedule is that all patients were eventually treated with the prednisolone/azathioprine combination, while using the conventional treatment schedule about a third of the children can maintain remission with very low-dose steroids alone. In addition, longer follow-up of the patients is necessary to establish possible long-term toxicity of cyclosporin.

Mycophenolate mofetil (MMF) has been successfully used in adult patients with type 1 AIH who were either intolerant of or not responsive to azathioprine.⁸ MMF is an inhibitor of purine nucleotide synthesis and has a mechanism of action similar to that of azathioprine.⁹ It is not hepatotoxic or nephrotoxic, and its main side-effects are diarrhoea, vomiting and bone marrow suppression. In our experience, the drug was able to resolve laboratory abnormalities in 5 of 12 children who did not tolerate or respond to azathioprine. In 4 others, it reduced serum aminotransferase levels to a degree that allowed a decrease in the dose of prednisolone. Only 3 patients did not respond to MMF, and the side-effects were minor apart from severe nausea and dizziness in one of them.

Children who present with acute hepatic failure pose a particularly difficult therapeutic problem. Although it has been reported that they may benefit from conventional immunosuppressive therapy,^{10,11} only 1 of the 6 children with acute liver failure in our own series responded to immunosuppression and survived without transplantation. Of the 4 LKM1-positive patients, 1 died before a donor organ could be found and 2 died soon after transplant. Encouraging results have been reported using cyclosporin A in LKM1-positive patients presenting with fulminant hepatitis,¹¹ but these results must be confirmed in a larger number of patients.

Autoimmune Sclerosing Cholangitis (ASC)

Clinical Features

Sclerosing cholangitis is an uncommon disorder, characterised by chronic inflammation and fibrosis of the intrahepatic and/or extrahepatic bile ducts. In childhood, sclerosing cholangitis may occur as an individual disease or develop in association with a wide variety of disorders, including Langerhans' cell histiocytosis, immunodeficiency, psoriasis, cystic fibrosis and chronic inflammatory bowel disease. An overlapping syndrome between AIH and sclerosing cholangitis has been reported in both adults¹² and children.^{13,14} In a prospective study over a period of 16 years, we have found that 27 of 55 children who presented with clinical and/or laboratory evidence of

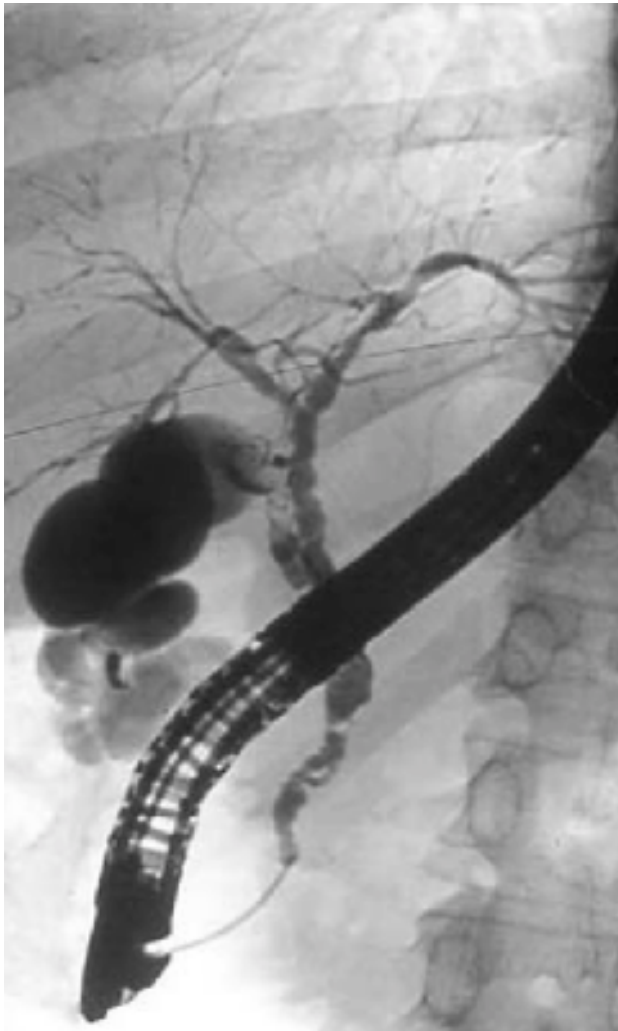


Fig. 2. Endoscopic cholangiography demonstrating widespread intra- and extra-hepatic changes.

AIH had evidence of sclerosing cholangitis when assessed by liver biopsy examination, cholangiography, sigmoidoscopy and rectal biopsy at presentation.¹⁵ Bile duct abnormalities on cholangiography were both intra- and extrahepatic in two-thirds of patients (Fig. 2) and intrahepatic in one-third. These patients were diagnosed as having ASC.

Of the 27 patients with ASC, 26 were seropositive for ANA and/or SMA, and 1 for LKM1.¹⁵ Fifty-five per cent were girls, and the mode of presentation was similar to that of 28 patients with typical AIH. Symptoms were those of acute hepatitis or chronic liver dysfunction. In some instances, the symptoms were absent and the diagnosis was revealed after the incidental discovery of abnormal liver tests. Inflammatory bowel disease was present in 44% of children with cholangiopathy, compared to 18% of those with typical AIH, and more than 75% of children with ASC

had greatly increased serum IgG levels. Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) were present in 74% of individuals with ASC compared to 36% of patients with typical AIH.

There was only a partial concordance between the histological and radiological findings, and 6 patients had histological features more compatible with AIH than sclerosing cholangitis.¹⁵ Interestingly, all patients fulfilled the criteria for the diagnosis of “definite” or “probable” AIH established by the International Autoimmune Hepatitis Group.² Indeed, the diagnosis of sclerosing cholangitis was possible only because of the cholangiographic studies.

Treatment

Children with ASC respond to the same immunosuppressive treatment described above for typical AIH.¹⁵ The liver test abnormalities resolved in almost 90% of our patients within a median of 2 months after starting treatment. This good response is in contrast to the outcome in adults with primary sclerosing cholangitis (PSC), who have no beneficial effects from corticosteroid treatment.^{16,17} PSC of adults, however, is usually diagnosed at an advanced stage and may be due to various aetiologies. Disappointing results with immunosuppressive agents have been reported in a small number of children with sclerosing cholangitis associated with autoimmune features, but these children may have had a more advanced disease than those recruited into our prospective study.¹⁴ Ursodeoxycholic acid (UDCA) was added to our treatment schedule in 1992 following preliminary reports of its value in the treatment of adult PSC.^{18,19} The small number of patients and the relatively short follow-up period do not allow us to determine whether treatment with UDCA from onset is successful in arresting the progression of ASC. In adults with well-established PSC, UDCA treatment has been disappointing, possibly because of its advanced stage at the time of diagnosis.²⁰

Follow-up liver biopsy assessments in our series have shown no progression to cirrhosis, although 1 patient did develop a vanishing bile duct syndrome. Follow-up endoscopic retrograde cholangiograms have shown static bile duct disease in half of our patients with ASC and progression of the bile duct abnormalities in the other half. Interestingly, one of the children with AIH who was followed prospectively developed sclerosing cholangitis 8 years after presentation despite treatment with corticosteroids and no biliary changes on several follow-up liver biopsy specimens. This experience suggests that AIH and ASC are part of the same pathogenic process and that prednisolone and azathioprine may not be as effective in controlling the bile duct component of the disease.

The medium-term prognosis of ASC is good.¹⁵ All patients in our series were alive after a median follow-up of 7 years.

Four patients with ASC, however, required liver transplantation after 2 to 11 years of observation (median interval of follow-up, 7 years). In contrast, liver transplantation has not been required by any of the 28 children with typical AIH who were followed up over the same period.

It is unclear if the juvenile autoimmune form of sclerosing cholangitis and AIH are 2 distinct entities or different aspects of the same condition. Akin to AIH, liver-specific autoantibodies, including antibodies to liver-specific lipoprotein, asialoglycoprotein receptor, alcohol dehydrogenase and soluble liver antigen are found in ASC.²¹⁻²³ In contrast to AIH, HLA DR3 occurs as commonly in patients with ASC as in healthy control subjects, while HLA DR4 occurs less commonly in both conditions compared to the controls.

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