Autoimmune Hepatitis, Sclerosing Cholangitis, and Autoimmune Sclerosing Cholangitis or Overlap Syndrome

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KEYWORDS

• Autoimmune hepatitis • Immunosuppression • Sclerosing cholangitis
• Autoimmune sclerosing cholangitis • Children

KEY POINTS

- Autoimmune hepatitis is a diagnosis of exclusion and there is a scoring system in place for complicated cases.
- Sclerosing cholangitis is seen most commonly in association with inflammatory bowel disease.
- Autoimmune sclerosing cholangitis is the overlap of clinical, biochemical, and histologic features of autoimmune hepatitis and sclerosing cholangitis, seen most commonly in children.
- Immunosuppression is the current management for autoimmune liver disease in children and ursodeoxycholic acid is used in those diagnosed with sclerosing cholangitis.

INTRODUCTION

Autoimmune liver disease in pediatrics encompasses autoimmune hepatitis (AIH), autoimmune overlap with sclerosing cholangitis (SC), recurrence of AIH after liver transplantation, and the development of de novo AIH post-transplantation in patients transplanted for indications other than AIH.[1] Syndromes associated with AIH include autoimmune polyendocrinopathy candidiasis ectodermal dystrophy, immune dysregulation polyendocrinopathy enteropathy X-linked syndrome, common variable immunodeficiency, and hyperimmunoglobulin M syndrome.[2] An autoimmune phenotype has been described in association with drugs, and nitrofurantoin and

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minocycline are the most commonly implicated.[3] This article focuses on AIH, SC, and autoimmune overlap with SC.

DEFINITION AND TYPES OF AUTOIMMUNE HEPATITIS

Typically, AIH is described as a chronic inflammatory condition of the liver characterized by elevated serum aminotransferases and immunoglobulin G (IgG), presence of non-organ specific autoantibodies, and interface hepatitis with lymphoplasmacytic infiltration in the absence of known etiologic factors. Type 1AIH is associated with antinuclear antibody (ANA) with or without smooth muscle antibody (SMA). Type 2 AIH is associated with liver kidney microsomal (LKM) antibody with or without anti-liver cytosol type 1. Both types 1 and 2 AIH may be associated with other types of autoimmune disease, including thyroiditis, celiac disease, and type 1 diabetes in up to 20% of patients. Family history of autoimmune disease is also reported to be present in up to 40% of patients with both types of AIH. The differences between types 1 and 2 AIH are illustrated in **Table 1**. Presence of soluble liver antigen signifies a worse prognosis in those with AIH.

Epidemiology and Pathogenesis

The prevalence of AIH has been reported as 1 per 200,000 in the US general population and 20 per 100,000 in female patients older than the age of 14 years in Spain.[4] The disease may be seen in all ethnic groups and ages but has a female preponderance. There is significant association with HLA DR3 and DR4. The pathogenesis of AIH is still not clear. The inflammation in the liver in AIH seems to be secondary to both cell-mediated (T-cell) and humoral (B-cell) activity. The stimulus that initiates the autoimmune inflammatory activity is unknown and may not be the same in all cases of AIH. Many viruses have been implicated and the identification of sequence homology between a virus and the target of antibodies has also been demonstrated in support of this mechanism of molecular mimicry.[5,6] The ability of T cells to proliferate is controlled by regulatory T (T-reg) cells, characterized by expression of CD4+, CD25 +, and nuclear expression of the forkhead transcription factor box P3 (FOXP3).[7] Reduced number and activity of these T-reg cells has been described in AIH.[8]

Table 1
Differences between type 1 and type 2 autoimmune hepatitis

	Type 1 AIH	Type 2 AIH
Age at presentation	Usually pubertal age	May present very early in life, much younger than type 1
Prevalence	Much more common than type 2	<1/3 of cases with AIH
Clinical features and course	Usually chronic	Acute liver failure presentation more common
Autoantibodies	ANA, SMA	LKM, Anti-liver cytosol type1
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy	No association	Association described
Histology	Cirrhosis more common	May have cell drop-out and necrosis in acute liver failure setting
Overlap with SC	Not uncommon	Very rare
Immunosuppression	May be weaned off	Need life-long immunosuppression

Scoring System

The first description of AIH appears in 1950 by Waldenstrom.[9] However, it was only after the discovery of the hepatitis C virus in 1989 that a scoring system was formulated to allow accurate diagnosis of AIH by the International Autoimmune Hepatitis group in Brighton, UK.[10] The scoring system has since been modified.[11] In the revised scoring system, points have been allocated to female gender, hepatitic liver chemistries, hypergammaglobulinemia, presence of autoantibodies (ANA, SMA, LKM), absence of viral markers, minimal alcohol intake, negative drug history, characteristic liver histology, possession of HLA DR3 or DR4 haplotype, presence of other defined antibodies, and complete or partial response to therapy. A score greater than 15 pre-treatment and greater than 17 post-treatment was considered definite AIH, whereas a score of 10 to 15 pre-treatment and12 to 17 post-treatment was considered as probable AIH.[11] This revised scoring system has been further simplified to facilitate use in clinical practice.[12]

Diagnosis

Children with AIH, may present similar to an acute viral hepatitis with jaundice, abdominal pain, be picked up incidentally, have an acute liver failure presentation, or with a complication of portal hypertension, including ascites and gastrointestinal bleeding. Given that the presentation is variable and can be at any age, it is important to investigate for AIH in a timely manner in any child presenting with liver disease. The physical examination of these children varies from unremarkable to jaundiced with hepatosplenomegaly, depending on severity of disease. Laboratory testing may show evidence of hypersplenism with low white cell count and/or thrombocytopenia, impaired synthetic function with prolonged international normalized ratio and low serum albumin, elevated serum aminotransferases and serum bilirubin, elevated IgG, and positive autoantibodies. Imaging may show an enlarged liver and/or spleen, with ascites in advanced cases. Liver biopsy is an important tool and the histology typically shows a lymphoplasmacytic infiltration spilling over the limiting plate at the interface of the portal tract and the hepatocytes, which was previously known as piecemeal necrosis and now as interface hepatitis (**Fig. 1**). Emperipolesis and rosette formation are significantly associated with an autoimmune diagnosis.[1] In acute liver failure, the characteristic histology is not seen because there may be extensive necrosis and multilobular collapse. It is essential to rule out other etiologic factors, including viral hepatitis (A, B, C and E), Wilson disease, and alpha1-antitrypsin deficiency, before making a diagnosis of AIH. The scoring system is useful in complex cases and to compare subjects in research settings.

Management

Immunosuppression is the mainstay of therapy. It is conventional to start therapy with a steroid bolus, prednisone 2 mg/kg (maximum 40–60 mg), and preferable to give an antacid. Azathioprine (AZA) is usually added as a steroid-sparing agent but the start time can vary. Some clinicians like to start AZA at the beginning with the prednisone, others prefer to reserve it for instances when the serum aminotransferases flare during the steroid taper. It is not recommended to start AZA in the beginning when there is an acute liver failure presentation or severe liver disease with cirrhosis because hepatotoxicity may occur. The author's (Kerkar) preference is to check the thiopurine methyl transferase (TPMT) enzyme while commencing the steroid bolus and then starting the AZA when the results of the genetic study are available. The dose of AZA typically used in children is 1 to 2 mg/kg/d (maximum 50 mg at the start) and then titrated according

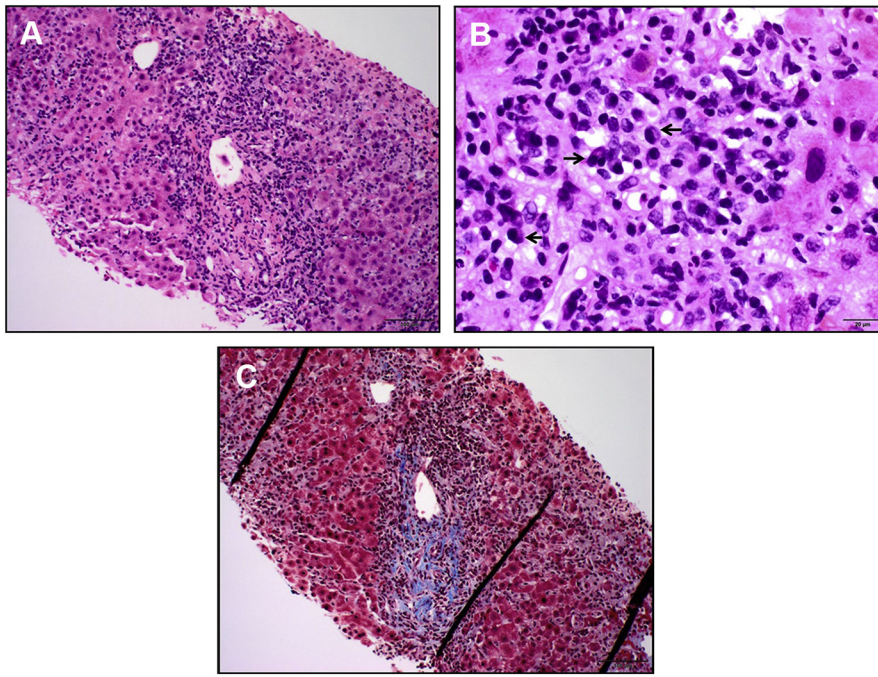

Fig. 1. (*A*, *B*) A portal tract is expanded by a chronic inflammatory infiltrate that includes plasma cells (seen at higher power in *B*, *arrows*) and extends beyond the limiting plate, consistent with interface hepatitis (hematoxylin-eosin, original magnification × 100). (*C*) Fibrosis that extends beyond the portal tract on trichrome stain (hematoxylin-eosin, original magnification × 400). (*Courtesy of* Philip J. Katzman, MD, University of Rochester Medical Center, Rochester, NY)

to the levels of the active metabolite, 6-thioguanine (6-TG). The dose of AZA may then be increased until 6-TG levels are between 240 to 400 pmol/8x10 (8) red blood cells, provided the levels of the hepatotoxic metabolite, 6-methylmercaptopurine (6-MMP) are below 5000 pmol/8 x10 (8) red blood cell.[13] In some situations when the dose of AZA is increased, instead of the 6-TG levels increasing, the levels of 6-MMP go up. Here, allopurinol may be used to divert the metabolism of AZA, so that 6-TG levels get to therapeutic levels without hepatoxicity.[14] High 6-TG levels can cause bone-marrow toxicity. Pancreatitis is an idiosyncratic adverse event of AZA and checking the TPMT enzyme does not preclude its occurrence. When 6-TG is in the therapeutic range and the serum aminotransferases are in normal range, it is possible to wean the patient off the steroids completely. Some clinicians prefer to keep the patient on a combination of low-dose prednisone with AZA. Given the importance of achieving the full growth potential of the child, many prefer AZA monotherapy whenever feasible.

Remission and Relapse

Remission in AIH is said to occur when there is disappearance of symptoms, normal serum aminotransferases, bilirubin, and IgG with normal hepatic tissue or inactive cirrhosis histologically.[15] Once remission is achieved and maintained for several years, effort is often made to wean the patient off immunosuppression. The latter should not be attempted during puberty when autoimmune flares are common. Also, weaning immunosuppression off completely is not recommended in type 2 AIH because disease is

more severe and relapse is almost inevitable. Relapse is defined as flare in serum aminotransferases after remission has been achieved. Usually, one has to repeat the liver biopsy and bolus the patient again with steroids. Checking adherence and reinforcing to the patient the importance of good adherence is essential for good outcomes.

Other Therapeutic Options

Mycophenolate mofetil (MMF) has been used successfully as rescue treatment in situations in which there have been adverse events with AZA or when AZA has not worked.[16] The adverse event profile of MMF includes gastrointestinal symptoms, bone marrow suppression, hair loss, and headaches. Budesonide may be a good option to consider when avoiding steroid side effects is the goal, because it has a high first-pass clearance in the liver. Budesonide, when used with AZA in a large multicenter study in adults, showed superior results to a combination of AZA with prednisone.[17] It is, however, recommended to not use budesonide alone as induction in AIH and to be aware that reactivation of AIH on budesonide monotherapy has been reported.[18] Calcineurin inhibitors (cyclosporine and tacrolimus) that are used as standard immunosuppression in transplant recipients to prevent rejection have been used successfully in controlling AIH.[11,19] Antitumor necrosis factor (TNF)-alpha has been used successfully as rescue treatment in difficult-to-treat AIH.[20] Recently, in a series of 11 children with juvenile autoimmune liver disease who received infliximab and/or adalimumab for their inflammatory bowel disease (IBD), all tolerated the treatment well without any impairment of liver function.[21] On the other hand, one must be aware that anti-TNF–related, drug-induced liver injury with autoimmune features have also been reported in children during management of IBD,[22] so careful monitoring of patients is necessary. Very recently, there have been reports in Japanese patients with AIH of using ursodeoxycholic acid (UDCA) monotherapy to successfully achieve and maintain remission[23]

Special Considerations

Autoimmune hepatitis with acute liver failure

In AIH presenting with acute liver failure and encephalopathy, medical management with immunosuppression is of little benefit and there is high risk of septic complications. The best option is to work the patient up for liver transplantation and list the patient. A trial of steroids may be tried cautiously in children, provided it is done by an experienced hepatologist in an institution with good intensive care facilities and liver transplantation capabilities. Success has been reported with immunosuppression in AIH with fulminant liver failure in some centers.[24,25]

Autoimmune hepatitis and liver transplantation

Liver transplantation is performed in 10% to 15% of children with AIH. Indications for transplantation include

1. Failure of medical treatment
2. Acute liver failure, particularly associated with encephalopathy
3. Development of hepatocellular carcinoma (rare).

AIH is the indication for transplantation in 2% to 3% of the liver transplants performed in the pediatric population in United States and Europe.[15] The patient and graft survival after liver transplantation are good and comparable to transplants for other indications. It is important to manage immunosuppression carefully after liver transplantation to minimize and possibly avoid recurrence of autoimmune disease in the allograft. Adding a third agent, AZA or MMF, to the calcineurin inhibitor and

prednisone is helpful in achieving this. The risk of recurrent AIH has been reported to be between 15% and 40%.[26,27] The incidence increases as the interval from transplant increases and when there is nonadherence or another reason (eg, high Epstein-Barr virus polymerase chain reaction) for being on reduced immunosuppression. De novo AIH is the development of the classic features of AIH in patients not transplanted for AIH.[28] This was first described in children in 1989 and since then there have been numerous reports of its occurrence in the pediatric and adult population.[29] Although it is a rare cause of graft dysfunction, early diagnosis and appropriate management can help save grafts and lives. Ability to diagnose this accurately and early is contingent on a high degree of suspicion and on requesting an autoimmune panel with serum IgG and autoantibodies at the time of performing a liver biopsy after liver transplantation. The liver biopsy will show classic changes of AIH (as previously described). When AIH is diagnosed post transplant, either recurrent or de novo, management is with a bolus of steroids and the addition of another immunosuppressive agent such as AZA or MMF. The steroid taper, however, is much slower than that used to treat rejection, in line with that used in therapy of classic AIH.

Natural History and Prognosis

The natural history and prognosis of AIH depends on severity of the disease and is also influenced by adherence to medical management. Children diagnosed at an early age, with a strong family history, and advanced changes on histology are likely to require lifelong immunosuppression and even liver transplantation. Similarly, those presenting with acute liver failure and encephalopathy are more likely to have mortality without transplantation than those with mild disease. Almost all children should achieve remission within the first year of therapy. They can achieve excellent quality of life if their disease is under control on minimal immunosuppression. Too-rapid attempts to wean off immunosuppression or non-adherence can cause a high risk of relapse. It is important to monitor serum aminotransferases and the autoimmune panel intermittently, after stopping immunosuppression, so that a flare can be picked up early. Children with type 1 AIH are much more likely to have sustained remission off immunosuppression than type 2 AIH. An overall survival of 82% was noted in 34 children with AIH over a 6-year study period.[30] Risk factors for mortality include weight loss, jaundice, coagulopathy, and the presence of LKM; cirrhosis at presentation did not seem to influence outcome in this cohort. Hepatocellular carcinoma is a known complication of end-stage liver disease. Development of hepatocellular carcinoma with AIH in children is extremely rare compared with adults. Surveillance with alpha-fetoprotein and ultrasound scan may be done in patients with AIH and cirrhosis.

PEDIATRIC SCLEROSING CHOLANGITIS

Introduction

SC is a rare, chronic disease that afflicts the hepatobiliary system. It is characterized by an inflammatory process, leading to progressive fibrosis of the intrahepatic and/or extrahepatic bile ducts. Ultimately, it progresses toward end-stage liver disease, liver failure, biliary cirrhosis, cholangiocarcinoma, or a combination of these.[31] SC is widely known as primary SC, particularly in adults. In general, the term primary is used when the etiologic factors are unknown. In pediatrics, SC may be associated with several conditions, including ABCB4 (MDR3) gene mutation, cystic fibrosis, immunodeficiency, and Langerhans cell histiocytosis.[1] There is also autosomal recessive neonatal SC and overlap with AIH, the latter is known as autoimmune SC (ASC) (see later discussion).

Epidemiology

The incidence and prevalence of pediatric SC are estimated to be 0.2 and 1.5 cases per 100,000 children, respectively.[32] These numbers might be an underestimation because SC is often insidious and has subtle symptoms in the early stages.[33] Because it may have variable clinical presentation, SC may be difficult to detect early, and diagnosis is often made when obvious symptoms are present or complications arise. SC is seen more frequently in male patients by 2-fold. In addition, an increased prevalence in SC among first-degree relatives (0.7%), and more so in siblings (1.5%), has also been shown.[34] SC is often seen concurrently with AIH in children. It is associated with IBD in approximately 76% of children, with ranges reported typically from 33% to 90%.[35–38]

Primary Sclerosing Cholangitis–Inflammatory Bowel Disease

In pediatrics, the SC associated with IBD is widely referred to as primary SC (PSC). In patients with PSC and IBD, ulcerative colitis (UC) seems to be more common than Crohn disease. Whereas up to 90% of patients with SC have a diagnosis of IBD, most reports estimate that only about 4% of patients with IBD also have a diagnosis of PSC.[39] Interestingly, studies with longer term follow-up of IBD demonstrate higher rates of PSC. For example, the population of subjects with UC studied by Lindberg and colleagues[40] noted the prevalence of PSC in IBD to be 9.8%, and the mean time of onset from UC to PSC was about 12 years. Similarly, in centers where screening tests were performed more frequently, higher rates of PSC were found.[41] These studies suggest that the overall prevalence of PSC-IBD may actually be higher than what has typically been reported.

The intestinal inflammation of PSC-IBD may be different than the inflammation of non–PSC-IBD. When compared with non–PSC-UC, patients with PSC-UC are more likely to have pancolitis.[42] Similarly, those with PSC and Crohn disease tend to have Crohn colitis and those with PSC-UC had lower rates of IBD-related hospital admission and colectomies, suggesting a milder course of bowel disease. Studies suggest that the severity of disease in IBD does not predict the severity of disease in PSC, nor does treatment of IBD affect the overall course of PSC.[43]

Small-Duct Sclerosing Cholangitis

A diagnosis of small-duct SC is made in patients with typical symptoms of cholestasis, with biliary changes on liver histology consistent with SC, but without visible bile duct abnormalities on either endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP).[44] The diagnosis of small-duct SC is more common in children (13%–36%) than in adults (5%).[45,46] Small-duct SC seems to have better prognosis overall compared with classic or large-duct SC[47] and does not seem to lead to cholangiocarcinoma unless it converts to large-duct SC. A subset of patients with small-duct SC will require liver transplantation; however, there have been reports of post-transplant recurrence.

Diagnosis

In children, SC tends to have insidious onset, so early diagnosis can be difficult. Therefore, SC tends to be diagnosed only when obvious symptomatology or laboratory or imaging test abnormalities are present. The symptoms can include abdominal pain; decreased appetite and weight loss; growth delay; deficiencies in fat-soluble vitamins A, D, E, and K; fatigue; fever; jaundice; and pruritus.[35] Intractable pruritus is less common in children but remains an important indication for liver transplantation.[48]

On physical examination, hepatomegaly, splenomegaly, and/or jaundice may be present. Elevations of serum aminotransferases and γ-glutamyl transferase (GGT) can be seen and are typically significantly higher in children than in adults. Whereas ALP elevation is a useful marker in adults, GGT is more accurate in children because ALP can be affected by bone growth. In addition, GGT is already being used for prognostic purposes in other pediatric cholestatic diseases such as biliary atresia or parenteral nutrition–associated liver disease.

Imaging, such as MRCP or ERCP can show irregularity of the bile duct wall, multifocal dilatations, and intermittent strictures of the bile duct, showing a beaded appearance. MRCP is more commonly used in the pediatric population compared with ERCP owing to its lack of radiation, non-invasiveness, and its accuracy rate of 85%, making it a good screening test. Due to its invasive nature, ERCP has a higher risk of adverse events such as pancreatitis; yet, it has a definitive role in the management of SC. First, it may be needed for diagnosis if MRCP is non-diagnostic. Second, it can be therapeutic via dilation of dominant strictures within the bile ducts. Third, it is used to screen for cholangiocarcinoma because the risk for developing it is 9% at 10 years and 19% at 20 years after diagnosis.[49]

Liver biopsy can characteristically show periductal onion skin fibrosis (**Fig. 2**) but this finding is neither pathognomonic nor universally present (only seen in up to 40% of cases).[50] However, liver biopsy is warranted in the diagnosis of AIH–autoimmune overlap with SC and small-duct SC and thus may be more useful in children than in adults.[51] In the diagnosis of SC, it is important to think about secondary causes of SC. These may include but are not limited to choledocholithiasis, infectious causes (ascending cholangitis, sepsis), immunodeficiency, neoplasm, congenital causes (Caroli disease), or biliary injury.[52]

Management

The treatment of PSC is mostly supportive because there is no known medication that can stop the progression of this disease. Medications that have been used for the treatment of PSC-IBD include UDCA and vancomycin. UDCA is a hydrophilic bile acid that is already being used for many cholestatic liver diseases in children. It can protect liver cells from damage by inhibiting intestinal absorption of hepatotoxic bile acids, as well as by stimulating bile flow and secretion of bile acids, thus limiting cellular injury. UDCA may also have anti-inflammatory or immunomodulatory effects. UDCA has been shown to improve liver chemistries and cholestasis.[53] Unfortunately, there is no evidence that UDCA can improve liver outcomes in children or adults. Furthermore, high dosages of UDCA (30 mg/kg/d) have been shown to be associated with a 2-fold risk of death or transplant.[54] Based on these data, high dosages of UDCA should be avoided in children but smaller dosages could have some use (up to 20 mg/kg/d in divided doses). Discontinuation of UDCA could lead to deterioration in liver biochemistries.[55]

Vancomycin is a bactericidal antibiotic that mainly alters gram-positive bacteria by binding to precursor units of the cell wall. It is poorly absorbed in the gut, so its main area of effect is within the intestinal lumen. Data for vancomycin usage are conflicting and more studies need to be done. Davies and colleagues[56] reported a series of 14 subjects in whom use of vancomycin (50 mg/kg/d, treatment durations were variable) led to normalization of liver transaminases, GGT, and erythrocyte sedimentation rate in noncirrhotic children. Those with cirrhosis showed improvement of the same laboratory values but without complete normalization. It is important to recognize that 13 of the 14 subjects did have signs of colitis. Adult data are less promising. When weighing the use of vancomycin, it is important to consider long-term consequences of contributing to vancomycin-resistant enterococci, which could lead to rapid development of secondary SC.[57]

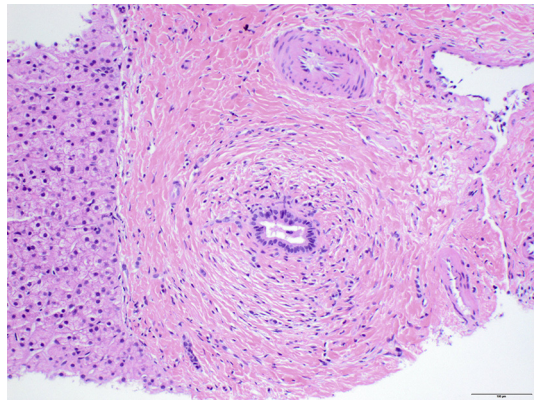

Fig. 2. Portal fibrosis with periductal concentric fibrosis and mild edema, also called "onion-skinning", is present in this liver needle core biopsy. These findings are consistent with primary sclerosing cholangitis (original magnification× 100). (*Courtesy of* Philip J. Katzman, MD, University of Rochester Medical Center, Rochester, NY)

ERCP can help to dilate dominant strictures. Balloon dilatation of dominant strictures could potentially slow down the development of end-stage liver disease and improve pre-transplant survival. Liver transplantation remains the definitive action for progressive SC and should be highly considered in patients with decompensated cirrhosis, hilar cholangiocarcinoma, intractable pruritus, or chronic cholangitis. Approximately 2% of all pediatric liver transplants are secondary to SC. However, SC can recur in about 20% of cases.[58] Survival of patients with liver transplantation are similar to survival rates of other organ transplants. There are differences in various medical societies regarding the screening of cholangiocarcinoma in patients with SC. Carbohydrate antigen 19-9 is the primary screening marker for cholangiocarcinoma, and carcinoembryonic antigen may also be abnormally elevated in 30% of patients with cholangiocarcinoma. However, although these tests may have high specificity, they have low sensitivity.[59]

Natural History and Outcomes

Descriptions of the natural history of pediatric SC are limited due to its relative rarity and a general lack of long-term follow-up studies. This led to the formation of a pediatric PSC consortium, which was a multicenter and international collaborative effort, enrolling 781 children as of 2017.[36] Data from the consortium showed that 38% of patients developed portal hypertension and 25% developed biliary complications after 10 years. Once these complications developed, the median survival rate with the native liver were 2.8 years and 3.5 years, respectively. In children, 1% developed cholangiocarcinoma. Event-free survival was 70% at 5 years and 53% at 10 years. The study also showed that high bilirubin, GGT, and high aspartate aminotransferase-to-platelet ratio typically led to worse outcomes. As in previous studies, subjects with PSC-IBD and small-duct SC had more favorable prognosis. In this study, long-term outcomes were not affected by age, gender, or AIH.

Pediatric Autoimmune Sclerosing Cholangitis or Overlap Syndrome

In hepatology, the term overlap syndrome is a clinical descriptor of various forms of autoimmune hepatobiliary diseases involving AIH, primary biliary cholangitis and PSC.[60] In pediatrics, the term ASC or overlap syndrome is being used to characterize patients with concomitant histologic and biochemical features of AIH, as well as those with SC.[1,61] In comparison with adults, ASC is described more commonly in children,

perhaps due to the lack of burn-out of autoimmune-mediated inflammation in children. In ASC, patients tend to have improvement in serum transaminases with immunosuppressive medications.[46,61]

Male and female patients are equally affected by ASC, unlike AIH in which there is a female predilection. Association with IBD is more frequent with ASC than with AIH. In 2001, the King's group published a study in which cholangiographic studies were performed at diagnosis in children and adolescents with AIH, and ASC was noted to be as prevalent as AIH.[61] Due to the high prevalence of ASC in the pediatric population, patients who are diagnosed with SC may benefit from being screened for AIH. In ASC, perinuclear antineutrophil cytoplasmic antibody (p-ANCA), ANA, and SMA are frequently positive and serum IgG is elevated.[1,62] If laboratory testing is positive, obtaining a liver biopsy to assess for features of AIH, such as interface hepatitis, can be helpful.[51] Similarly, children diagnosed with AIH should be screened for SC with imaging such as MRCP or ERCP, particularly when the serum GGT is elevated, which may allow earlier diagnosis of autoimmune SC.

The current scoring systems are not useful in distinguishing between AIH and ASC. A new scoring system has recently been proposed in the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines but requires validation.[1] In ASC, the immunosuppression therapy is similar to that used to treat AIH (see previous discussion). UDCA at a dosage of 10 mg/kg/d twice daily is added. It is not clear whether the biliary changes are reversible with this combination therapy. What is clear is that more multicenter studies are needed to better understand and manage ASC.

IgG subclasses should also be evaluated in patients with SC.[51] IgG4 is the least frequent IgG subclass, accounting for approximately 3% to 6% of total IgG in control subjects. Elevations of IgG4 may be found in a variety of conditions, notably autoimmune pancreatitis and IgG4-associated cholangitis (IAC).[63] Although it is important to rule out these entities as part of the workup for SC, up to 9% of SC patients have elevations of IgG4 but do not meet criteria for IAC. These patients seem to have a more aggressive phenotype and a shorter time to transplantation.[64]

SUMMARY

With the control of viral hepatitis, particularly hepatitis C, autoimmune liver disease is becoming an area of increased interest by both clinicians and researchers. It is important to have a high index of suspicion and screen appropriately for AIH because the spectrum of presentation is wide, from completely asymptomatic to acute liver failure. Ruling out other causes of liver disease and the presence of interface hepatitis on liver biopsy are key to making a diagnosis of AIH. Scoring systems are available for complicated cases or when diagnosis is in doubt. Management is with immunosuppression.

SC is rare in children. It has high morbidity and is progressive without a medical cure, leaving liver transplantation as the ultimate treatment despite potential recurrence of the disease posttransplantation. The diagnosis is made with imaging, laboratory tests, and sometimes liver biopsy, and by ruling out secondary causes. In children, compared with adults, there is a higher incidence of ASC and small-duct SC; hence liver biopsy may be of higher importance in children. There is a lower incidence of cholangiocarcinoma in pediatrics. The natural history of SC shows better prognosis in the IBD-PSC and small-duct subtypes. UDCA may improve liver biochemistries but does not seem to improve outcomes. Use of vancomycin lacks definitive data but, anecdotally, may be beneficial. There is overlap of AIH with SC, known as ASC or overlap syndrome, seen more commonly in children than adults.

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