Autoimmune Hepatitis and Sclerosing Cholangitis

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Introduction

Autoimmune hepatitis (AIH) and sclerosing cholangitis are major causes of liver disease in children and adolescents and should always be considered in the differential diagnosis of childhood hepatopathies. Both conditions have clinical and laboratory features, response to treatment and outcome different from their adult counterparts. A common form of sclerosing cholangitis in childhood has strong autoimmune features and is referred to as autoimmune sclerosing cholangitis (ASC). The presentation of AIH and sclerosing cholangitis is nonspecific and can mimic most other liver disorders. As prompt treatment, particularly in AIH, is life saving, it is imperative to suspect these conditions and perform appropriate investigations in all children who present with a cryptogenic liver disorder.

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Autoimmune Hepatitis

AIH is a progressive inflammatory liver disorder characterized serologically by high levels of transaminases and immunoglobulin G (IgG), and presence of autoantibodies, and histologically by interface hepatitis (Fig. 16.1a), in the absence of a known etiology [1]. In children and adolescents, AIH often presents acutely and has a more aggressive course than in adults. AIH usually responds satisfactorily to immunosuppressive treatment, even when it presents with features of acute liver failure [2]. If left untreated, it progresses rapidly to cirrhosis and liver failure. Seventy-five percent of patients are girls.

Two types of AIH are recognized: AIH type 1 (AIH-1), which also affects adults, is characterized by the presence of smooth muscle antibody (SMA) and/or antinuclear antibodies (ANA); AIH type 2 (AIH-2), which is mainly a pediatric condition, is positive for antibodies to liver-kidney microsomal type 1 (anti-LKM-1) [3] and/or anti-liver cytosol type 1 (anti-LC1) [4, 5].

AIH-1 accounts for two thirds of the cases and presents often around puberty, whereas AIH-2 tends to present at a younger age and also during infancy. IgG is usually raised at disease onset in both types, though 15 % of children with AIH-1 and 25 % of those with AIH-2 have normal levels. IgA deficiency is common in AIH-2 [3]. Severity of disease is similar in the two types, but anti-LKM-1-positive children have higher levels of bilirubin and transaminases at onset than those who are ANA/SMA positive and

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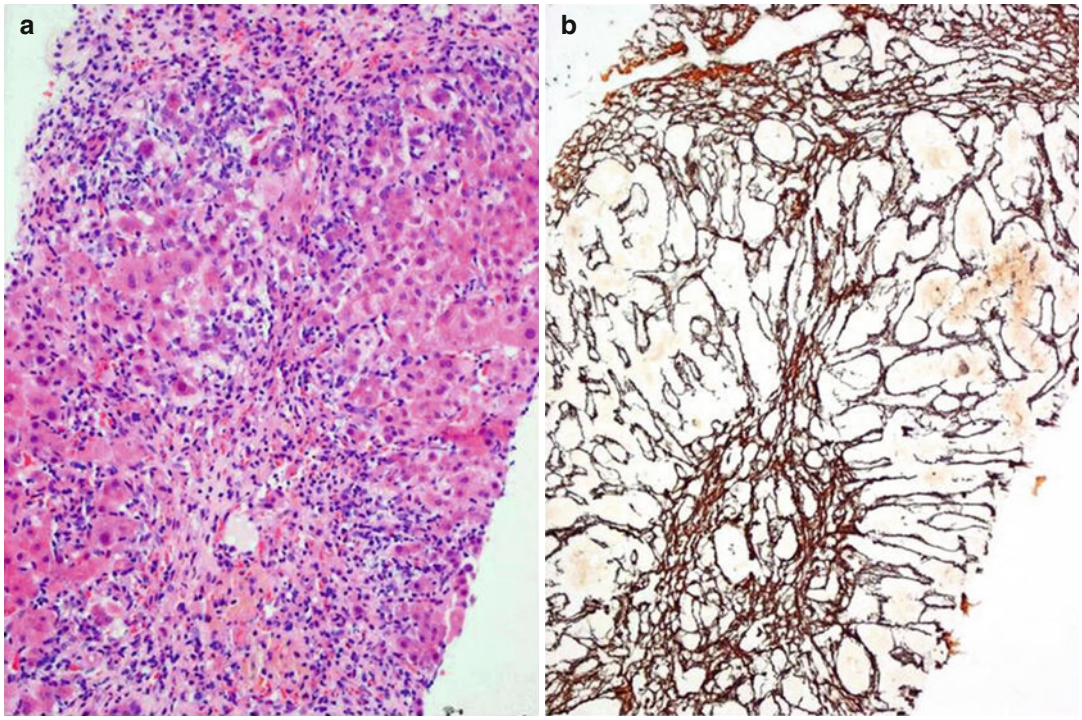

Fig. 16.1 Panel (**a**): portal and periportal lymphocyte and plasma cell infiltrate, extending to and disrupting the parenchymal limiting plate (interface hepatitis). Swollen hepatocytes, pyknotic necroses, and acinar inflammation are present. Hematoxylin and eosin staining. Panel (**b**): bridging collapse of the hepatic stroma following hepatocellular necrosis. Reticulin staining (Pictures kindly provided by Dr Alberto Quaglia)

present significantly more frequently with fulminant hepatic failure [3]. Excluding children with the fulminant presentation, a severely impaired hepatic synthetic function, as indicated by the presence of prolonged prothrombin time and hypoalbuminemia, is more common in AIH-1 than in AIH-2. The severity of interface hepatitis at diagnosis is similar in both types, but cirrhosis on initial biopsy is more frequent in AIH-1 than in AIH-2, suggesting a more chronic course of disease in the former. Progression to cirrhosis during treatment is more frequent in AIH-1.

In both types of AIH, a more severe disease course and a higher tendency to relapse are associated with the possession of antibodies to soluble liver antigen (SLA), which are present in approximately half of the patients with AIH-1 or AIH-2 at diagnosis (Table 16.1) [7, 9]. In both types, 20 % of patients have associated autoimmune disorders—including thyroiditis, vitiligo, type 1 diabetes, inflammatory bowel disease (IBD), and nephrotic syndrome—and 40 % have a family history of autoimmune disease (Table 16.1) [3].

There are three clinical patterns of AIH presentation [3]: (a) in at least 40 % of patients, the presentation is indistinguishable from that of an acute viral hepatitis (nonspecific symptoms of malaise, nausea/vomiting, anorexia, and abdominal pain, followed by jaundice, dark urine, and pale stools). Some children, particularly those who are anti-LKM-1 positive, develop acute hepatic failure with grade II to IV hepatic encephalopathy (fulminant hepatitis) within 2–8 weeks from onset of symptoms. (b) In 25–40 % of patients, the onset is insidious, with an illness characterized by progressive fatigue, relapsing jaundice, headache, anorexia, amenorrhea, and weight loss, lasting for several months and even years before diagnosis. (c) In about 10 % of patients, there is no history of jaundice, and the diagnosis follows presentation with complications of portal hypertension, such as

Table 16.1 Clinical, immunological, and histological features at presentation of autoimmune hepatitis type 1 (AIH-1), autoimmune hepatitis type 2 (AIH-2), and autoimmune sclerosing cholangitis (ASC) among patients referred to the King's College Hospital Tertiary Paediatric Liver Centre [3, 6]

	AIH-1	AIH-2	ASC
Median age in years	11	7	12
Females (%)	75	75	55
Mode of presentation (%)			
Acute hepatitis	47	40	37
Acute liver failure	3	25	0
Insidious onset	38	25	37
Complication of chronic liver disease	12	10	26
Associated immune diseases (%)	22	20	48
IBD (%)	20	12	44
Family history of autoimmune disease (%)	43	40	37
Bile duct changes on cholangiography (%)	0	0	100
ANA/SMA (%)	100	25	96
Anti-LKM-1 (%)	0	100	4
pANNA (%)	45	11	74
Anti-SLA (%)[a]	58	58	41
Increased IgG level (%)	84	75	89
Partial IgA deficiency (%)	9	45	5
Low C4 level (%)	89	83	70
Increased frequency of HLA *DR*0301*	Yes	No[b]	No
Increased frequency of HLA *DR*0701*	No	Yes	No
Increased frequency of HLA *DR*1301*	No	No	Yes
Histology			
Interface hepatitis (%)	92	94	60
Biliary features (%)	28	6	35

IBD inflammatory bowel disease, *ANA* antinuclear antibodies, *SMA* anti-smooth muscle antibody, *anti-LKM-1* anti-liver-kidney microsomal type 1 antibody, *pANNA* peripheral antinuclear neutrophil antibody, *anti-SLA* anti-soluble liver antigen antibody, *IgG* immunoglobulin G, *IgA* immunoglobulin A, *C4* C4 component of complement, *HLA* human leukocyte antigen

[a]Measured by radioligand assay [7]

[b]But increased in HLA *DR*0701* negative patients [8]

splenomegaly, hematemesis from esophageal varices, bleeding diathesis, chronic diarrhea, and weight loss.

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 liver disease not ascribable to more common pathologies. The course of the disease can be fluctuating, with flares and spontaneous remissions, a pattern that may result in delayed referral and diagnosis. The majority of children, however, on physical examination have clinical signs of an underlying chronic liver disease, including cutaneous stigmata (spider naevi, palmar erythema, leukonychia, striae), firm liver, and splenomegaly. At ultrasound, the liver parenchyma of these patients is often nodular and heterogeneous.

Epidemiology and Genetic Predisposition

The epidemiology of childhood AIH has not been studied. Data collected at the King's College Hospital Pediatric Hepatology tertiary referral center show an increase in the yearly incidence of juvenile autoimmune liver disease, only partially explained by a referral bias: In the 1990s, it represented 2.3 % of 400 children older than 4 months who were newly referred yearly; since 2000, the yearly incidence has increased to 12 %.

In northern Europe, pediatric AIH-1, similar to adult AIH, is associated with the possession of the human leukocyte antigen (HLA) *DRB1*03* [3, 10]. In contrast to adult patients, possession of *DRB1*04* does not predispose to AIH in childhood and can even exert a protective role [3]. AIH-2 is associated with possession of *DRB1*07* [8, 11] and, in DR7 negative patients, with possession of *DRB1*03* [8]. In Egypt, AIH-2 appears to be associated also with possession of *HLA-DRB1*15* [11]. In Brazil and in Egypt, the primary susceptibility allele for AIH-1 is *DRB1*1301*, but a secondary association with *DRB1*0301* has also been identified [11, 12]. Interestingly, in South America, possession of the HLA *DRB1*1301* allele not only predisposes to pediatric AIH-1, but is also associated with persistent infection with the endemic hepatitis A virus [13, 14]. Pediatric patients with AIH, whether anti-LKM-1 or ANA/SMA positive, have isolated partial deficiency of the HLA class

III complement component C4, which is genetically determined [15].

AIH-2 can be part of the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome, an autosomal recessive monogenic disorder [16, 17] in which the liver disease is reportedly present in over 20 % of cases [18, 19].

Diagnosis

The diagnosis of AIH is based on a series of inclusion and exclusion criteria [20, 21]. Liver biopsy is necessary to establish the diagnosis, the typical histological picture including a dense mononuclear and plasma cell infiltration of the portal areas, which expands into the liver lobule; destruction of the hepatocytes at the periphery of the lobule with erosion of the limiting plate ("interface hepatitis") (Fig. 16.1a); connective tissue collapse resulting from hepatocyte death and expanding from the portal area into the lobule ("bridging collapse") (Fig. 16.1b); and hepatic regeneration with "rosette" formation. In addition to the typical histology, other positive criteria include elevated serum transaminase and IgG levels and presence of ANA, SMA, or anti-LKM-1.

The diagnosis of AIH has been advanced by the scoring systems developed by the International Autoimmune Hepatitis Group (IAIHG) for adult patients [20, 21] where negative criteria such as evidence of infection with hepatitis B or C virus, Wilson disease, or alcohol, are taken into account in addition to the positive criteria mentioned above. The IAIHG scoring system was devised mainly for research purposes to allow ready comparison between series from different centers, but has also been used clinically, including in pediatric series. More recently, the IAIHG has published a simplified scoring system based on autoantibodies, IgG, histology, and exclusion of viral hepatitis that is better suited to clinical application [22]. However, neither scoring system is suitable to the juvenile form of the disease, where diagnostically relevant autoantibodies often have titers lower than the cutoff value considered positive in adults [23–25]. In addition, neither system can distinguish between AIH and ASC (see below) [6, 26], which can only be differentiated if a cholangiogram is performed at presentation.

A key diagnostic criterion for all AIH scoring systems is the detection of autoantibodies (ANA, SMA, and anti-LKM-1), which not only assists in the diagnosis, but also allows differentiation of AIH types. ANA and SMA that characterize AIH-1 and anti-LKM-1 that defines AIH-2 are practically mutually exclusive; in those rare instances when they are present simultaneously, the clinical course is similar to that of AIH-2 [27]. ANA, SMA, and anti-LKM-1 should be sought by indirect immunofluorescence using rodent stomach, kidney, and liver as substrate, as other techniques, e.g., commercially available ELISAs, remain to be fully validated [27]. In contrast to adults, in healthy children autoantibody reactivity is infrequent, so that titers of 1/20 for ANA and SMA and 1/10 for anti-LKM-1 are clinically relevant. Positivity for autoantibodies, however, is not sufficient for the diagnosis of AIH since they can be present, usually at low titer, in other liver disorders such as viral hepatitides [28, 29], Wilson disease [30], and nonalcoholic steatohepatitis [31].

Other autoantibodies less commonly tested but of diagnostic importance include anti-liver cytosol type 1 (LC-1), peripheral antinuclear neutrophil antibody (atypical pANCA or pANNA), and anti-SLA. Anti-LC-1, detected by indirect immunofluorescence, can be present on its own, but frequently occurs in association with anti-LKM-1, and is an additional marker for AIH-2 [5, 32]. pANNA is frequently found in AIH-1 and in ASC and is also common in IBD, while it is virtually absent in AIH-2. Anti-SLA, originally described as the hallmark of a third type of AIH [33], is also found in some 50 % of patients with AIH-1, AIH-2, and ASC, where it defines a more severe course [7]. Anti-SLA is not detectable by immunofluorescence, but the definition of its molecular target as UGA transfer RNA (tRNA) suppressor-associated antigenic protein (SepSecS) [34, 35] has enabled the establishment of molecularly based diagnostic assays. However, it should be noted that commercial

enzyme-linked immunosorbent assays (ELISAs) are less sensitive than radioligand assays available in research laboratories [7, 9].

There is a small proportion of patients with AIH without detectable autoantibodies. This condition, which responds to immunosuppression like the seropositive form, represents seronegative AIH [36], a rare type of AIH in adults, whose prevalence and clinical characteristics remain to be defined in children.

Treatment

Definition of Remission/Relapse

Remission is defined as clinical recovery, normal transaminase and IgG levels, negative or very low-titer autoantibodies by immunofluorescence (≤1:20 for ANA and SMA; ≤1:10 for anti-LKM-1), and histological resolution of inflammation. The histological response lags behind the biochemical response [37], and clinical/biochemical remission does not necessarily reflect histological resolution. After a mean duration of 4 years of treatment, improvement of the intensity of portal inflammation is observed in up to 95 % of AIH cases and is accompanied by an improvement of fibrosis scores [37]. Relapse is characterized by an increase of serum aminotransferase levels above normal values after remission has been achieved. Relapse during treatment is common, occurring in about 40 % of patients and requiring a temporary increase in the steroid dose [3]. An important role in relapse is played by nonadherence, particularly in adolescents [38]. In more aggressive cases, the risk of relapse is higher if steroids are administered on an alternate-day schedule, which is often instituted in the belief that it has a less negative effect on the child's growth. Small daily doses are more effective in maintaining disease control and minimize the need for high-dose steroid pulses during relapses (with consequent more severe side effects) and do not affect final height [39].

When to Treat

AIH should be suspected and sought in all children with evidence of liver disease after exclusion of infectious and metabolic etiologies. With the exception of a fulminant presentation with encephalopathy, where liver transplant is usually required, AIH responds satisfactorily to immunosuppressive treatment whatever the degree of liver impairment, with a reported remission rate exceeding 80 % [3, 6, 40, 41]. Treatment should be initiated promptly to avoid progression of disease.

The goals of treatment are to reduce or eliminate liver inflammation, to induce remission, to improve symptoms, and to prolong survival [42]. The rapidity and degree of the response depend on the disease severity at presentation. Though cirrhosis is found in between 44 and 80 % of children at the time at diagnosis, [3, 43] development of end-stage liver disease requiring liver transplantation is rare, most children remaining clinically stable, with a good quality of life on long-term treatment.

How to Treat

Standard Treatment

Conventional treatment of AIH consists of an initial dose of prednisolone (or prednisone) of 2 mg/kg/day (maximum 60 mg/day), which is gradually decreased over a period of 4–8 weeks, in parallel to the decline of transaminase levels, to a maintenance dose of 2.5–5 mg/day, depending on the child's age and weight [42, 44]. In most patients an 80 % decrease of the aminotransferase levels is achieved in the first 2 months, but their complete normalization may take several months [3]. During the first 6–8 weeks of treatment, liver function tests should be checked often to allow weekly dose adjustments, avoiding severe steroid side effects. In our center, azathioprine is added as a steroid-sparing agent if the transaminase levels stop decreasing on steroid treatment alone or in the presence of early serious steroid side effects (e.g., psychosis), 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 2.0–2.5 mg/kg/day until biochemical control is achieved. The timing for the addition of azathioprine varies in different centers. In some centers, azathioprine is added in all cases at a dose of 0.5–2 mg/kg/day after a few weeks of steroid treatment. Other centers use a combination of steroids and azathioprine from the

beginning, but caution is recommended because azathioprine can be hepatotoxic, particularly in severely jaundiced patients. Whatever the protocol, 85 % of the patients eventually require the addition of azathioprine.

Measurement of thiopurine methyltransferase activity level before initiating azathioprine therapy has been advocated to predict azathioprine toxicity. However, only patients with near-zero erythrocyte concentrations of thiopurine methyltransferase activity are at risk for myelosuppression during azathioprine treatment [45], and determination of the enzyme activity is warranted only when there is pre- or intra-treatment cytopenia, or the need of higher than conventional doses [46]. Measurement of the azathioprine metabolites 6-thioguanine and 6-methylmercaptopurine has been reported to help in identifying drug toxicity and nonadherence and in achieving a level of 6-thioguanine considered therapeutic for inflammatory bowel disease [47], though an ideal therapeutic level for AIH has not been determined.

Alternative Treatments

Induction of remission has been obtained in treatment-naïve children using cyclosporine A alone for 6 months, followed by the addition of prednisone and azathioprine. One month later the cyclosporine was discontinued [40, 41]. Cyclosporine was used at the dose of 4 mg/kg/day in three divided doses, increased if necessary every 2–3 days to achieve a whole blood concentration of 250 ± 50 ng/ml for 3 months. If there was clinical and biochemical response in the first months, cyclosporine was reduced to achieve a concentration of 200 ± 50 ng/ml for the following 3 months, before discontinuing it. Whether this mode of induction has any advantage over the standard treatment has yet to be evaluated in controlled studies.

Tacrolimus is a more potent immunosuppressive agent than cyclosporine, but it also has significant toxicity. There is limited evidence supporting its role as initial treatment of AIH apart from anecdotal reports in adults.

Budesonide has a hepatic first-pass clearance of >90 % of oral dose and fewer side effects than predniso(lo)ne, but cannot be used in cirrhotic patients, who represent a large proportion of AIH patients. In a large European study, a combination of budesonide and azathioprine had fewer adverse effects compared to medium-dose standard prednisone and azathioprine [48]. In this study, budesonide at a dose of 3 mg three times daily, decreased upon response, was compared with prednisone 40 mg once daily reduced per protocol irrespective of response. After 6 months of treatment, remission was achieved in 60 % of the budesonide group, but in only 39 % of the prednisone group, both percentages being worse than those achieved with standard treatment [3]. However, the results within the paediatric cohort of this study are disappointing, with similarly low remission rates in the budesonide/azthioprine and prednisone/azathioprine arms (16 % and 15 % after 6 months of treatment and 50 % and 42 % after 12 months of treatment respectively) [49]. The poor response rate to prednisolone/azathioprine in this study compared to that observed with standard treatment (80–90 %) is likely to depend on the low fixed initial dose of prednisone, decreased by protocol and not according to response, used in the trial [50]. Nevertheless, budesonide could be a valid alternative in selected non-cirrhotic patients who are at risk of adverse effects from steroids.

Maintenance with azathioprine monotherapy has been advocated once remission is achieved [51], but whether this is effective long term and whether it offers any benefit on possible side effects compared to low-dose prednisolone/azathioprine maintenance are unclear.

Treatment of Refractory Cases

Mycophenolate mofetil (MMF) is the prodrug of mycophenolic acid. Its effect on purine synthesis leads to decreased T- and B-lymphocyte proliferation. In patients (up to 10 %) in whom standard immunosuppression is unable to induce stable remission, or who are intolerant to azathioprine, MMF at a dose of 20 mg/kg twice daily (total daily dose 40 mg/kg), together with predniso(lo)ne, is successfully used [52]. If there is a persistent lack of response or if there is intolerance for MMF (headache, diarrhea, nausea, dizziness, hair loss, and neutropenia), the use of calcineurin inhibitors should be considered. In our center, tacrolimus, in combination with prednisolone,

has been successful in inducing remission in difficult-to-treat patients.

Duration of Treatment and Prognosis

The optimal duration of immunosuppressive treatment for AIH is unknown. Treatment withdrawal is successful only if there is histological resolution of inflammation. Hence, cessation of treatment should be considered if a liver biopsy shows minimal or no inflammatory changes after 1–2 years of normal liver function tests, normal IgG levels, and negative or low-titer autoantibodies. However, it is advisable not to attempt to withdraw treatment within 3 years of diagnosis or during or immediately before puberty, when relapses are more common. It has been reported that 20 % of patients with AIH-1 can successfully and permanently stop treatment, while this is rarely achieved in AIH-2 [3]. Long-term treatment is required for the majority of patients, and parents and patients should be counselled accordingly. In the pediatric setting, an important role in monitoring the response to treatment is the measurement of IgG levels and autoantibody titers, the fluctuation of which correlates with disease activity [53]. In particular, for patients with high IgG levels, their decrease is a reliable, objective, and inexpensive measure of disease control.

The prognosis of those children with AIH who respond to immunosuppressive treatment is generally good, with most patients surviving long term with excellent quality of life on low-dose medication. Development of end-stage liver disease requiring liver transplantation despite treatment, however, has been reported 8–14 years after diagnosis in 8.5 % of children with AIH [3].

Sclerosing Cholangitis

The term primary sclerosing cholangitis (PSC), used in adult patients, is not accurate to describe pediatric sclerosing cholangitis: "primary" denotes ignorance about etiology and pathogenesis, while in pediatrics [6, 54–57] there are well-defined forms of sclerosing cholangitis. In the neonatal period, pathological features of severe sclerosing cholangitis characterize biliary atresia as well as neonatal sclerosing cholangitis (NSC), a condition inherited in an autosomal recessive manner [58]. Some other inherited diseases and immunological defects may produce a clinical picture similar to adult PSC. For example, mild to moderate defects in the *ABCB4* (MDR3) gene are a likely cause of a number of cases of small duct PSC in children [59, 60]; moreover sclerosing cholangitis may complicate a wide variety of disorders, including primary and secondary immunodeficiencies, Langerhans cell histiocytosis, psoriasis, cystic fibrosis, reticulum cell sarcoma and sickle cell anaemia. Moreover, an overlap syndrome between AIH and sclerosing cholangitis, ASC, is significantly more common in children than in adults. In only a relatively small number of pediatric patients, sclerosing cholangitis occurs without any of the above defining features. The term of PSC should be confined to the latter.

With the increased usage of biliary imaging in the form of endoscopic retrograde cholangiopancreatography (ERCP), percutaneous cholangiography, and, more recently, noninvasive magnetic resonance cholangiography (MRCP), sclerosing cholangitis is diagnosed with increasing frequency in pediatric age and is an important cause of morbidity and mortality, accounting for some 2 % of the pediatric liver transplants in the USA between 1988 and 2008 [United Network for Organ Sharing (UNOS) Data Report—October 2009. http://www.unos.org/data/].

There are five relatively large studies of sclerosing cholangitis in childhood [6, 54–57] describing a total of 236 cases. In these reports the incidence of the various clinical forms of sclerosing cholangitis differs depending upon the year when and the center where the study was conducted, reflecting different study design, patterns of referral, and diagnostic protocols (Table 16.2). In four of these series, cholangiographic studies, performed by ERCP, percutaneous cholangiography, or, more recently, MRCP, were prompted by biochemical and/or histological features of cholestatic disease [53–56]. Interestingly, in the most recent series [56], where cholangiographic studies were mainly performed by MRCP, no radiological biliary involvement was detected, despite histological evidence of sclerosing cholangitis, in a high proportion

Table 16.2 Comparison of the different forms of sclerosing cholangitis in five published pediatric series

	Debray et al. [54]	Wilschanski et al. [55]	Gregorio et al. [6]	Feldstein et al. [56]	Miloh et al. [57]
Total number of patients	56	32	49	52	47
Immunodeficiency	8 (14 %)	2 (6 %)	6 (12 %)	0	0
Langerhans cell histiocytosis	14 (25 %)	0	2 (4 %)	0	0
Neonatal SC	15 (27 %)	0	5 (10 %)	0	0
Psoriasis	1 (2 %)	0	0	0	0
PSC	10 (18 %)	10 (31 %)	9 (18 %)	38 (73 %)	35 (75 %)
AIH/SC overlap	2 (4 %)	9 (28 %)	27 (55 %)	14 (27 %)	12 (25 %)
IBD	7 (13 %)	17 (53 %)	15 (31 %)	42 (81 %)	28 (59 %)
Ulcerative colitis	4	14	8	30	20
Crohn disease	3	3	3	8	8
Indeterminate colitis			4	4	

SC sclerosing cholangitis, *AIH* autoimmune hepatitis, *IBD* inflammatory bowel disease

(36 %) of patients ("small-duct PSC"). Whether this finding is due to a lower sensitivity of the MRCP compared to the ERCP in detecting biliary changes remains to be verified.

Our own study, published in 2001, differs from all the other series, as it was prospective and aimed at establishing the relative incidence of AIH and AIH/sclerosing cholangitis overlap syndrome (autoimmune sclerosing cholangitis, ASC) among children presenting with liver disease and positive autoimmune serology (autoantibodies; increased levels of IgG) [6], by performing cholangiograms at disease onset, irrespective of biochemical or histological evidence of cholestatic disease. Other forms of sclerosing cholangitis seen over the same period of observation were excluded from the prospective study.

In all published series, boys are more affected than girls, 20–40 % of patients have intrahepatic cholangiopathy with normal extrahepatic bile ducts, and IBD is strongly associated with the diagnosis of sclerosing cholangitis, being found in some 63 % overall [6, 54–57]. More than two thirds of the cases had ulcerative colitis. The prevalence of IBD was higher in those centers where surveillance enteroscopy was performed and 23 % of the cases presented after the diagnosis of sclerosing cholangitis and even in the absence of clinical symptoms of IBD. It is, therefore, advisable to consider diagnostic colonoscopy in children who are newly diagnosed with sclerosing cholangitis and to have a low threshold for performing this procedure in those who have symptoms consistent with IBD (e.g., diarrhea, growth failure, anemia).

Autoimmune Sclerosing Cholangitis

In all the pediatric series described above, sclerosing cholangitis is often associated with florid autoimmune features, including elevated titers of autoantibodies, in particular ANA and SMA; elevated IgG levels; and interface hepatitis (Table 16.1 and Fig. 16.2a) [6, 54–57]. Whether these children respond to immunosuppressive treatment and whether their prognosis is different from that of children with AIH is controversial. In an attempt to clarify this, the King's prospective study was initiated in 1984 and conducted over a period of 16 years [6]. Interim results were published in 2001, but the patient cohort is being followed up to date. In this study, all children with serological (i.e., positive autoantibodies, high IgG levels) and histological (i.e., interface hepatitis) features of autoimmune liver disease underwent a cholangiogram at the time of presentation, independently from the presence of biochemical or histological evidence of cholestasis. Surveillance enteroscopy to investigate for possible IBD was

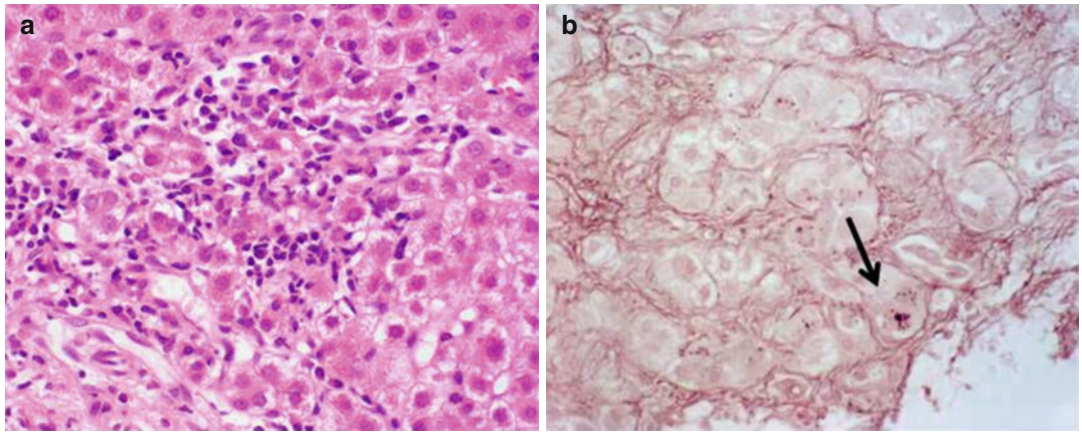

Fig. 16.2 Panel (**a**): portal plasma cell infiltrate in a child with autoimmune sclerosing cholangitis. Hematoxylin and eosin staining. Panel (**b**): orcein staining of the same biopsy shows copper-associated protein deposition (*arrow*) suggesting chronic cholestasis (Pictures kindly provided by Dr Yoh Zen)

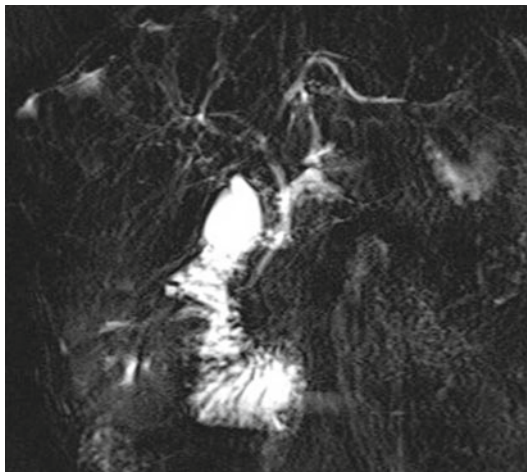

Fig. 16.3 Magnetic resonance cholangiography of a child with autoimmune sclerosing cholangitis showing a diffuse cholangiopathy with ductal changes in both lobes. The extrahepatic bile ducts have normal appearance

performed in all cases, independently from symptoms. Approximately 50 % of the patients enrolled in this prospective study had alterations of the bile ducts characteristic of sclerosing cholangitis, although they were generally less advanced than those observed in adult PSC (Fig. 16.3) and were diagnosed as having ASC. A quarter of the children with ASC, despite abnormal cholangiograms, had no histological features that suggested bile duct involvement, and the diagnosis of sclerosing cholangitis was only possible because of the cholangiographic studies. Virtually all ASC patients were seropositive for ANA and/or SMA. In contrast to AIH, which had a clear female preponderance, ASC was diagnosed in a similar proportion of boys and girls. The mode of presentation of ASC was similar to that of AIH-1. Inflammatory bowel disease was present in 45 % of children with ASC compared to 20 % of those with typical AIH, and 90 % of children with ASC had greatly increased serum IgG levels. At the time of presentation, standard liver function tests did not help in discriminating between AIH and ASC, although the alkaline phosphatase/aspartate aminotransferase ratio was significantly higher in ASC (Table 16.3). pANNA was present in 74 % of patients with ASC compared with 45 % of patients with AIH-1 and 11 % of those with AIH-2. Anti-SLA was found in some 50 % of patients with ASC, and also in this condition it defines a more severe disease course [7]. Evolution from AIH to ASC was documented in one patient during the published prospective series [6] and has been observed in two further patients during follow-up [62], suggesting that AIH and ASC are part of the same pathogenic process.

Clinical, laboratory, and histological features of types 1 and 2 AIH and ASC are compared in Tables 16.1 and 16.3.

Currently, in our center imaging of the biliary system by MRCP, followed by ERCP if MRCP is

Table 16.3 Biochemical indices at presentation in children with autoimmune hepatitis (AIH) and autoimmune sclerosing cholangitis (ASC) referred to the King's College Hospital Tertiary Paediatric Liver Centre [3, 6]

	AIH	ASC
Bilirubin (nv < 20 μmol/l)	35 (4–306)	20 (4–179)
Albumin (nv > 35 g/l)	35 (25–47)	39 (27–54)
AST (nv < 50 IU/l)	333 (24–4,830)	102 (18–1,215)
INR (<1.2)	1.2 (0.96–2.5)	1.1 (0.9–1.6)
GGT (nv < 50 IU/l)	76 (29–383)	129 (13–948)
AP (nv < 350 IU/l)	356 (131–878)	303 (104–1,710)
AP/AST ratio	1.14 (0.05–14.75)	3.96 (0.20–14.20)

Modified from [61]
AST aspartate aminotransferase, *INR* international normalized prothrombin ratio, *GGT* gamma glutamyl transpeptidase, *AP* alkaline phosphatase, *nv* normal values

Table 16.4 Response to treatment and outcome in patients with autoimmune hepatitis type 1 (AIH-1), autoimmune hepatitis type 2 (AIH-2), and autoimmune sclerosing cholangitis (ASC) treated at the King's College Hospital Tertiary Paediatric Liver Centre [3, 6, 62]

	AIH-1	AIH-2	ASC
Remission rate (%)	97	87	89
Median time to remission (months)	6	9	2
Relapse rate (%)	42	46	45
Cessation of treatment (%)	19	0	5
Liver transplant rate (%)	6	13	23
Disease recurrence posttransplant (%)	0	0	67

Modified from [61]

not informative, as well as colonoscopy is part of the evaluation of all children with liver disease associated with autoimmune features.

The IAIHG scoring systems for the diagnosis of AIH, as currently formulated, do not distinguish AIH from ASC [6, 26], as they do not include cholangiographic investigations at presentation.

HLA studies have shown that in the UK susceptibility to ASC is conferred by the possession of HLA *DRB1*1301* [13].

Treatment and Prognosis

Treatment and prognosis of sclerosing cholangitis depends on the underlying pathology. Management of sclerosing cholangitis associated to immunodeficiency syndromes, LCH, or metabolic/genetic disorders is closely related to the ability of controlling the primary disease. For sclerosing cholangitis without associated pathologies, no standard mode of treatment is presently advocated [63]. Based on a reported beneficial effect in adult PSC, ursodeoxycholic acid (UDCA) is used also for the treatment of childhood sclerosing cholangitis, but whether it is helpful in arresting the progression of the bile duct disease remains to be established. In adults with PSC, high-dose UDCA was reported as more beneficial than standard doses [64], but a randomized double-blind controlled study from the Mayo Clinic shows that high-dose UDCA has a negative effect [65]. It is prudent, therefore, to use doses not higher than 15–20 mg/kg/day.

A beneficial effect of oral vancomycin (500 mg tds) has been reported in 14 patients with sclerosing cholangitis and IBD [66]. All patients showed improvement of liver function tests and erythrocyte sedimentation rate, which was more marked in those without cirrhosis. These results await confirmation in a larger number of patients. Whether vancomycin acts through its antibiotic or immunomodulatory [67] properties remains to be elucidated.

The King's prospective study shows that ASC responds well to the same immunosuppressive treatment described above for AIH if started early, with resolution of liver test abnormalities within a few months in most patients (Table 16.4), but the medium- to long-term prognosis of ASC is worse than that of AIH because of progression of bile duct disease despite treatment in some 50 % of patients, with 20 % of them eventually requiring liver transplantation (Table 16.4) [6, 62]. Similarly, in the series by Miloh et al [57], though all patients with overlap AIH/sclerosing cholangitis syndrome were reported to have a favorable biochemical response to immunosuppression and UDCA treatment, 25 % required liver transplantation during the 12-year observation period. Response to immunosuppressive drugs

was less satisfactory in sclerosing cholangitis patients with autoimmune features described by Wilschanski et al. [55] and Feldstein et al. [56], possibly because of long-standing liver disease before starting treatment.

Reactivation of the liver disease often follows flares of the intestinal disease in sclerosing cholangitis patients with IBD. It is therefore essential to control efficiently the bowel disease to avoid progression of liver disease.

Liver Transplantation

Liver transplantation is indicated in patients with AIH who present with fulminant hepatic failure (with encephalopathy) and in patients with AIH or sclerosing cholangitis who develop end-stage liver disease despite treatment. The latter is more likely when established cirrhosis is present at diagnosis or if there is a long history of liver disease before the start of treatment. Approximately 10 % of children with AIH and 20 % of those with sclerosing cholangitis require liver transplantation (Table 16.4). After transplantation, recurrent AIH has been described in about 20 % of cases [68] and recurrent sclerosing cholangitis in 27 % of transplanted patients in Feldstein's series [56], but in as many as 67 % of the patients with ASC followed up prospectively at King's [62]. Diagnosis of recurrence is based on biochemical abnormalities, presence of autoantibodies, interface hepatitis on liver histology, steroid dependence, and, for sclerosing cholangitis, presence of cholangiopathy. Recurrence may occur even years after transplantation, and consequently maintenance of steroid-based immunosuppression at a higher dose than that used for patients not transplanted for autoimmune liver disease is generally recommended. While recurrence of AIH does not usually affect posttransplant outcome, recurrence of ASC leads to retransplantation in a high proportion of patients [62]. Recurrence of sclerosing cholangitis after transplantation appears to be associated to uncontrolled IBD [69]. In this context it is of interest that PSC recurrence in adults with IBD can be prevented by pre-liver transplant colectomy [70–72].

De Novo Autoimmune Hepatitis After Liver Transplantation

In the late 1990s, it was observed that AIH can arise de novo after liver transplantation in children who had not been transplanted for autoimmune liver disease. The characteristic of this condition is a histological picture of interface hepatitis and multilobular collapse associated with increased IgG levels and positive autoantibodies. These include ANA, SMA, and classical anti-LKM-1, but also atypical anti-LKM-1, staining the renal tubules but not the liver. After the original report [73], de novo AIH after liver transplant has been confirmed by several studies both in adult and pediatric patients [74, 75] [76]. Importantly, treatment with prednisolone and azathioprine using the same schedule for classical AIH, concomitant with reduction of the calcineurin inhibitor dose, is highly effective in de novo AIH, leading to excellent graft and patient survival. It is of interest that these patients do not respond satisfactorily to the standard antirejection treatment schedule, making it essential to reach an early diagnosis to avoid graft loss. Rapamycin has been reported to be effective in difficult-to-treat patients [77].

Conclusion

Over the past two decades, there has been a sharp increase in the diagnosis of both AIH and sclerosing cholangitis in children. Whether this is due to a real increase in prevalence or to an increased awareness of these conditions remains to be clarified. If diagnosed and treated early, AIH has an excellent prognosis, with only a minority of the children who achieve remission with immunosuppression requiring liver transplantation 10–20 years after presentation. The prognosis is worse in patients with sclerosing cholangitis, in whom a higher proportion requires transplantation medium term and in whom the risk of disease recurrence after transplant is very high, particularly for those who have strong autoimmune features and associated inflammatory bowel disease. A better understanding of the pathogenic mechanisms leading to AIH and sclerosing cholangitis will hopefully lead to a targeted, more efficient, and less toxic therapeutic approach.

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