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Invited Review

Autoimmune Hepatitis

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ABSTRACT

Autoimmune hepatitis is characterized by inflammatory liver histology, circulating nonorgan-specific autoantibodies, and increased levels of immunoglobulin G, in the absence of a known etiology. Two types of juvenile autoimmune hepatitis (AIH) are recognized according to seropositivity for smooth muscle and/or anti-nuclear antibody (AIH type 1) or liver kidney microsomal antibody (AIH type 2). There is a female predominance in both. AIH type 2 presents more acutely, at a younger age and commonly with immunoglobulin A deficiency, whereas 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 the 2 groups. Immunosuppressive treatment with steroids and azathioprine, which should be instituted promptly to avoid progression to cirrhosis, induces remission in 80% of cases. Relapses are common, often due to nonadherence. Drugs effective in refractory cases include cyclosporine and mycophenolate mofetil. Long-term treatment is usually required, with only some 20% of AIH type 1 patients able to discontinue therapy successfully. In childhood, sclerosing cholangitis with strong autoimmune features, including interface hepatitis and serological features identical to AIH type 1, is as prevalent as AIH, but it affects boys and girls equally. Differential diagnosis relies on cholangiographic studies. In autoimmune sclerosing cholangitis liver parenchymal damage responds satisfactorily to immunosuppressive treatment, whereas bile duct disease tends to progress. In this article we review the state of the art of diagnosis, monitoring, and treatment for children with AIH. ***JPGN 49:158–164, 2009.*** **Key Words:** Autoimmune hepatitis—hepatitis—Immunosuppression—Liver disease—Pediatrics. © 2009 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Autoimmune hepatitis (AIH) is a progressive inflammatory liver disorder affecting mainly females, characterized serologically by high levels of transaminases and immunoglobulin G (IgG), and presence of autoantibodies, and histologically by interface hepatitis, in the absence of a known etiology (1) (Fig. 1). Laboratory and histological features of AIH are at times associated with bile duct disease typical of primary sclerosing cholangitis. This overlap syndrome is referred to as autoimmune sclerosing cholangitis (ASC) (2).

AIH is divided into 2 types according to the autoantibody profile: type 1 is positive for anti-nuclear (ANA) and/or anti-smooth muscle (SMA) antibody, type 2 is positive for anti-liver kidney microsomal antibody type 1 (anti-LKM-1). AIH responds satisfactorily to immunosuppressive treatment. If left untreated, it generally progresses rapidly to cirrhosis and liver failure.

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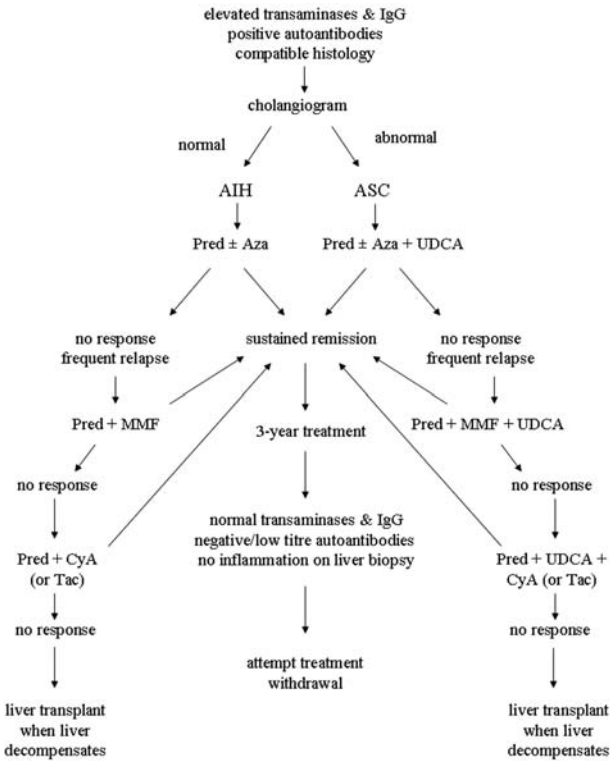

FIG. 1. Flowchart for treatment decision making in children with autoimmune liver disease.

Most patients are diagnosed before the age of 18 years and 75% are girls, the peak incidence of the disease being before puberty. The epidemiology of childhood AIH is unknown, but type 1 AIH accounts for two thirds of the cases and presents usually during adolescence, whereas type 2 AIH presents at a younger age and also during infancy. Immunoglobulin G is usually raised at presentation in both types, although 15% of children with AIH type 1 and 25% of those with AIH type 2 have normal levels (3). Immunoglobulin A deficiency is common in AIH type 2 (3). Severity of disease is similar in the 2 types. Anti-LKM-1–positive patients, however, have a higher tendency to present as acute liver failure. Both types are often associated with autoimmune disorders (about 20%) and a family history of autoimmune disease (40%) (3). Type 2 AIH can be part of the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome, an autosomal recessive genetic disorder in which the liver disease is reportedly present in some 20% of cases (4).

The main issues related to AIH are identification of etiopathogenic factors that may lead to its prevention; interpretation of liver autoimmune serology and diagnostic criteria in children; treatment, including type of drugs, length and criteria for stopping it, alternative drugs for refractory cases; and management of posttransplant recurrent, and de novo autoimmune hepatitis.

Discussion of the possible pathogenic mechanisms leading to AIH that may in the future be manipulated to prevent the disease is beyond the scope of the current review, which concentrates on diagnosis and management.

DIAGNOSTIC CRITERIA

Diagnosis of AIH is based on a series of positive and negative criteria (5,6) (Table 1). 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''); and connective tissue collapse resulting from hepatocyte death and expanding from the portal area into the lobule (''bridging collapse''); 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 criteria developed by the International Autoimmune Hepatitis Group (IAIHG) (5,6), in which negative criteria such as evidence of infection with hepatitis B or C virus or Wilson disease and alcohol, among others, are taken into account in addition to the positive criteria mentioned above. The International Autoimmune Hepatitis Group has provided a useful scoring system for the diagnosis of AIH for research purposes. A simplified scoring system, easier to use in clinical practice and on the basis of autoantibodies, IgG, histology, and exclusion of viral hepatitis has been published recently (7). A limitation of all of these scoring

TABLE 1. *Criteria for the diagnosis of autoimmune hepatitis in childhood*

Elevated transaminases	
Positive autoantibodies	ANA and/or SMA (titer $\geq$1:20) = type 1 AIH Anti-LKM1 (titer $\geq$1:10) = type 2 AIH Anti-LC1 = type 2 AIH Anti-SLA = present in type 1 or 2 AIH or in isolation
Elevated immunoglobulin G	
Liver biopsy	Interface hepatitis Multilobular collapse
Exclusion of viral hepatitis	
Exclusion of Wilson disease	
Normal cholangiogram (nuclear magnetic resonance or retrograde cholangiography)	

AIH = autoimmune hepatitis, ANA = antinuclear antibody, anti-LKM-1 = anti-liver/kidney microsomal antibody type 1, anti-LC1 = anti-liver cytosol type 1 antibody, anti-SLA = anti-soluble liver antigen antibody, SMA = anti-smooth muscle antibody.

TABLE 2. *Methods, associations, and reactants for autoantibodies in autoimmune liver disease*

Autoantibody	Conventional method of detection	Molecularly based assays	Disease association	Molecular target(s)
ANA	IIF	N/A	AIH-1; ASC	Multiple targets, particularly chromatin
SMA	IIF	ELISA	AIH-1; ASC	Microfilaments (actin?), intermediate filaments (vimentin, etc)
Anti-LKM-1	IIF*	ELISA, IB, RIA	AIH-2; HCV infection (5%)	Cytochrome P450 2D6
Anti-LC1	IIF, DID, CIE	ELISA, RIA	AIH-2	Formiminotransferase cyclodeaminase
Anti-SLA	Inhibition ELISA	ELISA, IB, RIA	AIH-1; AIH-2 and AIH negative for other reactivities	tRNP(Ser)Sec
Atypical pANCA (pANNA)	IIF	N/A	AIH-1; ASC	Unidentified antigen(s) at nuclear periphery
AMA	IIF*	ELISA, IB, RIA	Primary biliary cirrhosis	E2 subunits of 2-oxo-acid dehydrogenase complexes, particularly PDC-E2

AIH = autoimmune hepatitis, AMA = anti-mitochondrial antibody, ANA = anti-nuclear antibody, anti-LC1 = anti-liver cytosol type 1 antibody, anti-LKM-1 = anti-liver/kidney microsomal antibody type 1, anti-SLA = anti-soluble liver antigen antibody, ASC = autoimmune sclerosing cholangitis, CIE = counterimmunoelectrophoresis, DID = double dimension immunodiffusion, ELISA = enzyme-linked immunosorbent assay, HCV = hepatitis C virus, IB = immunoblot, IIF = indirect immunofluorescence, N/A = not available, pANCA = perinuclear anti-neutrophil cytoplasmic antibody, pANNA = perinuclear anti-neutrophil antibody, RIA = radioimmunoprecipitation assay, SMA = anti-smooth muscle antibody.

*Anti-LKM-1 and AMA both stain renal tubules and are frequently confused (1).

systems, however, is that they have been produced for adult patients and need to be adapted to children.

A key diagnostic criterion for all scoring systems is the detection of ANA, SMA, and anti-LKM-1 (Table 2). Autoantibody detection not only assists in the diagnosis but also allows differentiation of AIH types. Autoantibodies to nuclei and SMA that characterize type 1 AIH and anti-LKM-1 that defines type 2 AIH are practically mutually exclusive; in those rare instances in which they are present simultaneously, the clinical course is similar to that of AIH type 2 (8).

It is important to note that positivity for autoantibodies is not sufficient for the diagnosis of AIH because they can be present, usually at low titer, in other liver disorders such as viral hepatitides (9,10), Wilson disease (11), and nonalcoholic steatohepatitis (12).

The technique that should be used for routine testing of autoantibodies relevant to AIH is indirect immunofluorescence on a freshly prepared rodent substrate (8). This substrate should include kidney, liver, and stomach tissue to allow the detection of ANA, SMA, anti-LKM-1, as well as anti-liver cytosol type 1 (anti-LC-1), a second antibody defining type 2 AIH, and anti-mitochondrial antibody (AMA), the serological hallmark of primary biliary cirrhosis, which is only rarely associated with AIH in childhood. Recognition and interpretation of the immunofluorescence patterns is not always straightforward because it is operator dependent. Moreover, the relative rarity of AIH occasionally leads to errors in autoantibody reporting, particularly for those less frequently encountered such as anti-LKM-1, whose pattern is often confused with AMA. Problems in laboratory reporting and clinical interpretation of results are not only dependent on insufficient standardization of the tests but also on a degree of unfamiliarity of some clinicians with the disease spectrum of AIH. In regard to standardization, guidelines have been given by the IAIHG serology committee (8). An important concept is that significant titers of diagnostic autoantibodies differ in adult and pediatric patients. Because healthy adults may show reactivity at the conventional starting serum dilution of 1/10, the arbitrary dilution of 1/40 has been considered clinically significant by the IAIHG. In contrast, autoantibody reactivity in healthy children is infrequent, so that titers of 1/20 for ANA and SMA and 1/10 for anti-LKM-1 are clinically relevant. In this context, it is important to note that the use of commercially available tissue samples for the detection of autoantibodies is not recommended because these sections, fixed for achieving long shelf life, are of variable quality, hindering the recognition of diagnostic autoantibodies at low titer. It is advisable for the laboratory to report any level of positivity from 1/10 in children and 1/40 in adults, and for the attending physician to interpret the result within the clinical context.

On a freshly prepared rodent substrate, ANA is readily detectable as a nuclear staining in kidney, stomach, and liver. In the liver, the ANA pattern may be detected as homogeneous, or coarsely or finely speckled. In most but not all cases of AIH the pattern is homogeneous. To obtain a much clearer and more reliable definition of the nuclear pattern, human epithelial type 2 cells that have prominent nuclei are used. Human epithelial type 2 cells, however, should not be used for screening purposes, because nuclear reactivity to these cells is frequent at low serum dilution in the normal population (13), including in healthy children (14).

Smooth muscle antibody is detected on kidney, stomach, and liver, where it stains the walls of the arteries. On the renal substrate, it is possible to visualize the V (vessels), G (glomeruli), and T (tubules) patterns. The VG and VGT patterns are more specific for AIH than

the V pattern. The VGT pattern corresponds to the ''F actin'' or microfilament (MF) pattern observed using cultured fibroblasts as substrate. Neither the VGT nor the anti-MF patterns are, however, entirely specific for the diagnosis of AIH type 1 and some 20% of SMA positive AIH type 1 patients do not have the anti-MF/VGT pattern. The absence, therefore, of anti-actin SMA does not exclude the diagnosis of AIH (15).

Anti-LKM-1 stains brightly the liver cell cytoplasm and the P3 portion of the renal tubules, but does not stain gastric parietal cells. Anti-LKM-1 is often confused with AMA because both autoantibodies stain liver and kidney. However, in contrast to anti-LKM-1, AMA also stains the gastric parietal cells. The identification of the molecular targets of anti-LKM-1, such as cytochrome P4502D6 (CYP2D6), and of AMA, such as enzymes of the 2-oxo-acid dehydrogenase complexes, has led to the establishment of immunoassays on the basis of the use of the recombinant or purified antigens. Commercially available enzyme-linked immunosorbent assays are accurate for the detection of anti-LKM-1, at least in the context of AIH type 2, and reasonably accurate for the detection of AMA. Therefore, if a doubt remains after examination by immunofluorescence, this can be resolved by the use of molecularly based immunoassays.

Other autoantibodies less commonly tested but of diagnostic importance include those to liver cytosol type 1 (LC-1), antineutrophil cytoplasm (ANCA), and soluble liver antigen (SLA). Anti-LC-1, which can be present on its own, but frequently occurs in association with anti-LKM-1, is an additional marker for AIH type 2 and targets formimino-transferase cyclodeaminase (16). Antineutrophil cytoplasmic antibody can also be positive in autoimmune hepatitis. There are 3 types of ANCA, namely cytoplasmic, perinuclear, and atypical perinuclear, the target of which is a peripheral nuclear and not cytoplasmic perinuclear antigen (hence the suggested name of peripheral anti-nuclear neutrophil antibody [pANNA]). The type found in AIH type 1 is pANNA, which is also found in inflammatory bowel disease and sclerosing cholangitis, whereas it is virtually absent in AIH type 2. Anti-SLA that was originally described as the hallmark of a type 3 of AIH (17) is also found in 50% of patients with AIH type 1 and type 2, where it defines a more severe course (18). The molecular target of anti-SLA is UGA transfer RNA suppressor-associated antigenic protein (tRNP(Ser)Sec) (19,20). Molecularly based diagnostic assays have become available, but their full evaluation is still under way (Table 2).

After assessment of all of the specificities described above, 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 (5,6,21), a rare form of AIH in adults, whose prevalence and clinical characteristics remain to be defined in children.

In pediatrics, primary sclerosing cholangitis is often associated with florid autoimmune features, including elevated titers of autoantibodies, in particular ANA and SMA, elevated IgG, and interface hepatitis (2). Because these features are shared in common with AIH and are often not accompanied by elevated alkaline phosphatase or γ-glutamyl transpeptidase levels at disease onset, the diagnosis of sclerosing cholangitis relies on cholangiographic studies. In the absence of cholangiographic studies at presentation many of these children are diagnosed and treated as AIH, although the diagnosis of sclerosing cholangitis may become apparent during follow-up. This condition, referred to as ASC, is as prevalent as AIH type 1 in childhood, but in contrast to AIH it affects boys and girls equally (2). Autoimmune sclerosing cholangitis responds satisfactorily to immunosuppression, at least in regard to the parenchymal inflammation, if treatment is started early. Current IAIHG criteria do not allow distinction between AIH and ASC.

TREATMENT

Definition of Remission/Relapse

Remission is defined as complete clinical recovery, normal transaminase and IgG levels, negative or extremely low titer autoantibodies, and histological resolution of inflammation. The histological response lags behind the biochemical response (22–24) 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 cases and is accompanied by an improvement of the fibrosis scores (22). Relapse is characterized by increase of serum aminotransferase levels 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. An important role in relapse is played by nonadherence, which is common, particularly in adolescents (25). In more aggressive cases, the risk of relapse is higher if steroids are administered on an alternate-day schedule, which is often instituted because it may have 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 the consequent more severe adverse effects) and do not affect final height (26).

When to Treat

AIH should be suspected and sought in all children with evidence of liver disease after exclusion of infectious and metabolic etiologies. AIH is exquisitely responsive to immunosuppression and treatment should be initiated promptly to avoid progression of disease. The

goal of treatment is to reduce or eliminate liver inflammation, induce remission, improve symptoms, and prolong survival (27,28). The rapidity and degree of the response depends on the disease severity at presentation. Although cirrhosis is found between 44% and 80% of children at the time of diagnosis (3,29,30), mortality is low and most children remain clinically stable, with a good quality of life on long-term treatment.

How to Treat

With the exception of a fulminant presentation with encephalopathy, AIH responds satisfactorily to immunosuppressive treatment whatever the degree of liver impairment, with a reported remission rate around 80% (Fig. 1).

Standard Treatment

Conventional treatment of AIH consists of prednisolone (or prednisone) $2\,mg \cdot kg^{-1} \cdot day^{-1}$ (maximum 40–60 mg/day), which is gradually decreased over a period of 4 to 8 weeks in parallel to the decline of transaminase levels, to a maintenance dose of 2.5 to 5 mg/day (31–33). 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 (31,34). During the first 6 to 8 weeks of treatment, liver function tests should be checked weekly to allow frequent dose adjustments, avoiding severe steroid adverse effects. The timing for the addition of azathioprine as a steroid-sparing agent varies according to the protocols used in different centers. In some, azathioprine is added only in the presence of serious steroid adverse effects, or if the transaminase levels stop decreasing on steroid treatment alone, at a starting dose of $0.5\,mg \cdot kg^{-1} \cdot day^{-1}$, which in the absence of signs of toxicity is increased up to a maximum of 2.0 to $2.5\,mg \cdot kg^{-1} \cdot day^{-1}$ until biochemical control is achieved. In other centers azathioprine is added at a dose of 0.5 to $2\,mg \cdot kg^{-1} \cdot day^{-1}$ after a few weeks of steroid treatment, when the serum aminotransferase levels begin to decrease. Whatever the protocol, 85% of the patients eventually require the addition of azathioprine. Some 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.

Measurement of thiopurine methyltransferase activity level before initiating azathioprine therapy has been advocated to predict azathioprine metabolism and toxicity (34). 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 (35), although an ideal therapeutic level for AIH has not been determined.

Alternative Treatment

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 is discontinued (36,37). Cyclosporine is used at the dose of $4\,mg \cdot kg^{-1} \cdot day^{-1}$ in 3 divided doses, increased if necessary every 2 to 3 days to achieve a whole blood concentration of 250 ± 50 ng/mL for 3 months. If there is clinical and biochemical response in the first months, then cyclosporine is 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 in the treatment of AIH apart from anecdotal reports in adults.

Treatment of Refractory Cases

Mycophenolate mofetil 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, mycophenolate mofetil at a dose of 20 mg/kg twice daily, together with prednisolone, is successfully used (38). If there is a persistent absence of response or if there is intolerance of mycophenolate mofetil (headache, diarrhea, nausea, dizziness, hair loss, and neutropenia), then the use of calcineurin inhibitors should be considered. Tacrolimus may also be useful in combination with prednisolone as second-line therapy.

Other Treatments

No data are available on the effectiveness of budesonide or ursodeoxycholic acid (UDCA) in childhood AIH.

Treatment of Autoimmune Sclerosing Cholangitis

Autoimmune sclerosing cholangitis responds to the same immunosuppressive treatment described above for AIH. However, although steroids and azathioprine are beneficial in abating the parenchymal inflammatory lesions, they appear to be less effective in controlling the bile duct disease. UDCA is usually added to steroids and azathioprine for the treatment of ASC, but whether it is helpful in arresting the progression of the bile duct disease remains to be established. In adults with primary sclerosing cholangitis high-dose UDCA has been reported as more beneficial than standard doses (39), but a randomized double-blind controlled study presented as a late-breaking abstract by the Mayo Clinic group at the 50th

American Association for the Study of Liver Disease meeting (October 31–November 4, 2008, San Francisco) shows that high-dose UDCA has a negative long-term effect. It is prudent, therefore, to use doses not higher than $15\,mg \cdot kg^{-1} \cdot day^{-1}$. ASC is often associated with inflammatory bowel disease, which should be investigated even in the absence of symptoms and appropriately treated.

Duration of Treatment and Prognosis

The optimal duration of immunosuppressive treatment of AIH is unknown. Treatment withdrawal is successful only if there is histological resolution of inflammation. Hence, cessation of treatment should considered if a liver biopsy shows minimal or no inflammatory changes after 1 to 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 type 1 can successfully and permanently stop treatment, whereas this is rarely achieved in AIH type 2 (3). Long-term treatment is required for the majority of patients and parents and patients should be counseled accordingly. In the pediatric setting, an important role in monitoring the response to treatment is the measurement of autoantibody titers and IgG levels, the fluctuation of which correlates with disease activity (40). 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 to 14 years after diagnosis in 8.5% of children with AIH (3).

Liver Transplantation

Liver transplantation is indicated in patients who present with fulminant hepatic failure (with encephalopathy) and those who develop end-stage liver disease. The latter is more likely when established cirrhosis is present at diagnosis, or if there is a long history of disease before the start of treatment. Approximately 10% to 20% of children with AIH require liver transplantation. After transplantation, recurrent AIH may develop in about 20% of cases (41). Diagnosis is based on biochemical abnormalities, presence of autoantibodies, interface hepatitis on liver histology, and/or steroid dependence. Recurrence may occur even years after transplantation, and consequently maintenance of steroid-based immunosuppression at a higher dose than what is used for patients nontransplanted for AIH is generally recommended. Additionally, a form of graft dysfunction called de novo AIH, associated with positive autoantibodies, high IgG, histological features of interface hepatitis, and responsiveness to the standard treatment of AIH (but not to antirejection regimens), has been described in 6% to 10% of children receiving transplantation for nonautoimmune disorders (42,43).

SUMMARY

AIH is a progressive inflammatory liver disorder affecting mainly girls. It is divided in 2 types according to autoantibody positivity: SMA/ANA characterize AIH type 1 and anti-LKM1 antibodies AIH type 2. Even low titers of autoantibodies are diagnostic in pediatric age. Liver biopsy is required to establish the diagnosis. A juvenile form of sclerosing cholangitis has strong autoimmune features and resembles AIH type 1, differentiation between the 2 conditions being possible only by cholangiography.

Treatment should be instituted as soon as possible to avoid progression of disease and consists of prednisolone (or prednisone), to which azathioprine is added. Steroids should be weaned as tolerated over 6 to 12 months to the lowest dose able to maintain remission. Discontinuation of therapy could be considered after 1 to 2 years of complete remission if a liver biopsy shows no evidence of inflammation.

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