FEATURE ARTICLE

Autoimmune Hepatitis in Children
Saumya Pathak, MD; and Deepak Kamat, MD, PhD

ABSTRACT

Autoimmune hepatitis (AIH) is an immune-mediated, inflammatory liver disease. Clinical presentation of AIH in children is highly variable. It can present acutely, chronically, or silently. There are two main types of AIH—type 1 and type 2, which are differentiated and defined by the presence of specific autoantibodies. AIH eventually progresses to cirrhosis when left untreated, and occasionally even with treatment. AIH must be suspected and excluded in all children presenting with signs of acute, prolonged, or severe liver disease. The diagnosis of AIH is made by a combination of clinical manifestations, laboratory evaluation, histopathology, and the exclusion of other more common liver diseases. The best outcome for AIH is dependent on early diagnosis as well as early initiation of immunosuppressant therapy. [Pediatr Ann. 2018;47(2):e81-e86.]

DEFINITION

Autoimmune hepatitis (AIH) is a liver disorder that is immune-mediated and progressive in nature. It is characterized by the presence of circulating autoantibodies (immunoglobulin G [IgG]) and hypergamma-globulinemia.1 The clinical presentation of AIH is very diverse, affecting both children and adults, and more commonly affecting girls and women. AIH has a more aggressive course in the pediatric population, and initiation of early treatment is key to remission and avoidance of development of cirrhosis or liver failure.2 This article discusses the epidemiology, clinical manifestation, diagnostic evaluation, management, and prognosis of this uncommon condition in children.

Waldenstrom4 first described this disease in 1950. He observed elevated serum IgG levels and positive antinuclear antibodies (ANA) in a group of young women with a severe form of worsening hepatitis, leading him to wonder whether a disruption of the immune system was the cause of the hepatic disease in these women.

There are two types of juvenile AIH. Patients with AIH type 1 (AIH-1) are sero-positive for ANA and/or anti-smooth muscle antibody (anti-SMA), and patients with AIH type 2 (AIH-2) are sero-positive for anti-liver kidney microsomal type 1 antibody (anti-LKM-1) and/or for anti-liver cytosol type 1 antibody (anti-LC-1).2,5

EPIDEMIOLOGY

Prior to the 1990s, estimations of AIH in children had been inaccurate because there was not a standard method of diagnosis. Due to this lack of standardization, studies included other hepatic diseases in their prevalence estimations.6 The International Autoimmune Hepatitis Group (IAIHG) created a standard scoring system for diagnosing adults with AIH, and this scoring system was quickly adopted in the pediatric world. Since the IAIHG scoring system was released, different countries have calculated nationwide incidence and prevalence, but epidemiological studies are still limited. Boberg7 states that the incidence of AIH-1 among people (adult and children) of white origin in Europe and North America ranges from 0.1 to 1.9 per 100,000 per year. According to Verma et al.,8 the worldwide prevalence of AIH is 2 to 17 per 100,000 children. It is noted however, that clinical manifestations and outcomes of AIH do vary

---

Saumya Pathak, MD, is a Pediatric Resident Physician, Children’s Hospital of Michigan. Deepak Kamat, MD, PhD, is a Professor of Pediatrics, Vice Chair of Education, Department of Pediatrics, Wayne State University; and the Designated Institutional Official, Children’s Hospital of Michigan.

Address correspondence to Deepak Kamat, MD, PhD, Children’s Hospital of Michigan, 3901 Beaumien Boulevard, Detroit, MI 48201; email: dkmamat@med.wayne.edu.

Disclosure: The authors have no relevant financial relationships to disclose.
doi:10.3928/19382359-20180126-01
among ethnic groups, based primarily on adult studies. For example adult Hispanics with AIH had the highest prevalence of cirrhosis, and Asians had poorer survival outcomes. Also, AIH appears to be uncommon among Asian children compared with white children.

AIH more commonly affects females more than males (sex ratio, 4:1) (49%-96%). The disease has been reported to affect people from infancy to age 75 years, and the highest incidence rate is in people aged 10 to 30 years. Studies in white children show the median age of diagnosis to be 12.9 years. AIH-1 affects people of all ages, whereas AIH-2 is more common in younger children and infants. AIH-1 more commonly affects adolescents (two-thirds of all type 1 cases), and these patients present more often with cirrhosis, whereas AIH-2 is more common in younger children and presents with acute-onset liver failure. In children, either type of AIH can also be associated with autoimmune sclerosing cholangitis. It is also important to remember that AIH is strongly associated with other autoimmune diseases.

ETIOLOGY

The etiology of the disease is thought to be multifactorial (ie, environmental, genetic, immunologic). However, the initial insult that triggers the onset of inflammation is not yet known. Environmental factors may initiate a production of autoreactive CD4 and CD8 T-cells, leading to the production of autoantibodies. AIH in children has been associated with genetic markers, further strengthening the genetic predisposition and susceptibility for developing this autoimmune disease. The genes studied are associated with major histocompatibility complex II and specifically related to genes of human leukocyte antigen, which encode DRB1 alleles that are involved in peptide antigen presentation to CD4 T-cells. Various DRB alleles have been found to be associated with susceptibility to AIH (DRB1*1301, DRB1*0301, DRB1*1401, DRB1*0404, DRB1*0405, DRB1*0701, DRB1*0201). These alleles could be the markers of susceptibility, opening new possibilities for diagnosis, disease monitoring, prognostication, and gene-related therapy in the future.

CLINICAL PRESENTATION

Approximately 40% of patients with AIH present with the same symptoms as those of acute viral hepatitis: fatigue, tiredness, nausea, vomiting, jaundice, dark urine, pale stool, fever, and itching. Therefore, this acute severe presentation can be mistaken for a viral or toxic hepatitis. Acute AIH should be suspected in any child diagnosed with acute hepatitis without an identifiable etiology and/or that is not resolved after 4 to 6 weeks. This type of acute presentation is more common in AIH-2.

Another 40% of pediatric cases present with a gradual, subtler onset in which there is progressive fatigue, intermittent jaundice, and weight loss, all occurring months before the diagnosis is made. These children present with advanced disease in which they have evidence of chronic liver disease, including hepatosplenomegaly, spider veins, collateral circulation, ascites, and/or gastrointestinal bleeding.

There is one more form of presentation of AIH, and that is when it is diagnosed in a “presymptomatic” stage. Here, elevated transaminase levels are found on routine laboratory evaluation but the patient shows no clinical symptoms of disease.

It is important to remember that any type of AIH will naturally progress to cirrhosis when left untreated, and sometimes it will progress even with treatment. In summary, AIH must be suspected and excluded from all children presenting with clinical manifestations of acute, prolonged, or severe liver disease.

DIAGNOSIS

The diagnosis of AIH is made by a combination of clinical manifestations, laboratory evaluation, histopathology, and the exclusion of other common liver diseases. The clinical presentation is often the first clue that leads the physician to consider AIH as a possibility. However, as discussed earlier, the clinical manifestations of AIH vary greatly; therefore, the diagnosis in children can be difficult and is usually delayed.

Due to the rarity of AIH, common causes of hepatitis should be excluded first. Some of these common conditions include viral hepatitis (including hepatitis A, B, and C), Wilson’s disease, autoimmune sclerosing cholangitis, drug-induced hepatitis, alcoholic hepatitis (rare and dependent on the age group), alpha-1 antitrypsin deficiency, and nonalcoholic fatty liver disease. Generally, these viral, hereditary, metabolic, cholestatic, or drug-induced conditions may result in acute or chronic hepatitis in children.

AIH is characterized by three main findings: (1) high levels of transaminases and IgG and presence of autoantibodies, (2) presence of interface hepatitis on histology, and (3) absence of a known etiology for hepatitis.

Standard diagnostic criteria for AIH were first established in adults, and were created by the IAIH in 1993. This original scoring system was modified, simplified, and then extended to the pediatric population. The IAIHG proposed a simplified scoring system in 2007 for use in the pediatric population that includes four parameters: (1) presence of autoantibodies, (2) IgG
level, (3) liver histological findings, and (4) absence of viral hepatitis.

For the laboratory diagnosis of AIH, serum transaminases, serum IgG level, and AIH-related autoantibodies (ANA, SMA, anti-LKM-1, Anti-LC1, and anti-soluble liver antigen antibody [anti-SLA]) should be checked. Elevated levels of aspartate and alanine aminotransferases are usually the first laboratory abnormalities that are observed in AIH. Circulating serum IgG is also generally found to be elevated. Autoantibodies help differentiate between AIH-1 and AIH-2, along with helping to establish the diagnosis. As described above, ANA and/or SMA are positive in AIH-1, whereas anti-LKM-1 and/or anti-LC-1 antibodies are positive in AIH-2.

Each antibody found to be positive is not pathognomonic for AIH but is found to target a different antigen or component of the hepatocyte/liver in AIH. ANA targets the nuclear components of cells and is thought to be present in AIH due to hepatocyte injury. However, the mechanism that leads to positive ANA in AIH is not clearly understood. A positive ANA is present in other autoimmune and non-autoimmune diseases.

SMA targets components of actin and other components of the cytoskeleton, and thus it is seen to attack the smooth muscles of the vessels, glomeruli, and tubules of the liver. Anti-LKM-1 stains hepatocellular cytoplasm and renal tubules (hence the name). It is positive in AIH-2 and in patients with hepatitis C infection. Anti-LC-1 binds to the folate-metabolizing enzyme formimino transferase cycloaminase, which is highly prevalent in the liver. It can be used as a marker of hepatocellular inflammation in AIH. Lastly, anti-SLA is highly specific for AIH and identifies patients with severe disease and worst prognoses. It targets a transfer RNA suppressor-associated antigenic protein.

Because clinical manifestations are so variable and presence of serum autoantibodies and elevated IgG levels are very nonspecific, histologic evidence is necessary for the diagnosis of AIH. Regardless of clinical presentation, at the time of diagnosis 33% of patients have histologic evidence of hepatic cirrhosis on microscopic examination. These chronic histologic findings are common in AIH-1. Histologic findings that suggest AIH are described as interface hepatitis and/or multilobular hepatitis. Interface hepatitis is characterized by dense inflammatory lymphocytes and plasma cells that infiltrate the portal tracts, swelling of hepatocytes, and necrosis. Multilobular hepatitis is seen in acute disease or relapses and presents as necrosis and “rosette” formations. Rosettes are used to describe hepatocytes that form gland-like clusters when viewed through a microscope. These two histologic findings are not pathognomonic for AIH but are commonly seen, and thus help in the diagnosis.

Ferri et al. concluded that although the simplified scoring system includes histology as a criterion, and a liver biopsy should be performed prior to starting immunosuppressive therapy, the initiation of treatment in highly suspected patients should not be delayed if the biopsy cannot be performed. Liver biopsy can eventually be done when possible.

Pediatric studies on the validation of diagnostic criteria done by Mileti et al., Ebbeson and Schreiber, and Hiejima et al., showed that neither the original scoring system nor the simplified criteria could differentiate between primary sclerosing cholangitis (PSC) and AIH; therefore, a negative cholangiogram study was added to the diagnostic criteria to rule out PSC. Another important addition to the pediatric scoring system was that autoantibodies used for diagnosis have lower titers in children than in adults. Titers of 1:20 for ANA and 1:10 for anti-LKM-1 should be considered significant in children. Furthermore, when evaluating results of the autoantibodies, these studies show that titers of 1:20 could be false-negative results or falsely low at the time of diagnosis; thus, if clinical history and physical examination are suggestive of the diagnosis of AIH, a negative autoantibody result should not exclude the diagnosis of AIH. Similarly, Gregorio et al. stated that if the serum autoantibodies (ANA, SMA, LKM-1) used for diagnosis are not present at the time of diagnosis, AIH could not be excluded. A small number (5.8%) of their patients became positive for the autoantibodies at follow-up visits. Similarly, they point out that normal IgG values at diagnosis also do not exclude AIH in children, as elevated levels of IgG were absent in 20% of the patients at the time of diagnosis.

MANAGEMENT

Prior to the use of immunosuppressant therapy, 40% of patients with severe disease died within 6 months from the time of diagnosis. Those who survived developed cirrhosis and portal hypertension with a high rate of mortality at the 10-year mark from the time of diagnosis. The standard treatment for AIH in children is immunosuppression using corticosteroids and azathioprine. Corticosteroids should be initiated as soon as the diagnosis is established. The com-
bination of these two medications has a remission rate of about 80%.11

Corticosteroids and azathioprine work together but via different pathways. Prednisone gets converted to prednisolone, which enters the nucleus and inhibits cytokine transcription, leading to reduced proinflammatory cytokine production and T-cell activation. Azathioprine also gets converted to its active form of 6-thioguanine, which blocks purine nucleotide synthesis during the cell cycle, thus reducing lymphocyte production.26

Prednisone is initiated with the goal of achieving reduction of transaminase levels by 80% within first 8 weeks.26 After being treated with prednisone for 6 to 9 months, 75% to 90% of patients are able to achieve normal liver function.11 Weekly liver enzymes are checked in this early period, and steroid doses are regulated accordingly. Due to the long list of side effects of prednisone, azathioprine is usually added to lower the steroid dosage. Azathioprine reduces the steroid-related side effects and likely increases compliance.

Timing of initiation of azathioprine varies between medical centers, but the two most commonly listed times are when there are serious adverse effects from steroids or, if using steroids alone, when the level of transaminases cease to decrease.26 One important note is that azathioprine is potentially hepatotoxic; thus, in the acute-onset form of AIH, this drug can worsen the liver disease. Monitoring for signs of toxicity is crucial. Side effects of azathioprine include pancreatitis, cytopenia, and flu-like symptoms. A low dose of the corticosteroid and azathioprine is continued until remission.26

Remission in AIH is defined as when transaminase and IgG levels have normalized and there are none or only low-titer autoantibodies detected. Histological normalization is much slower than these laboratory results, and thus is not included in the definition of remission. In AIH-1, after 3 years of remission and histologic resolution of disease, it is possible to slowly discontinue treatment as long as there is close laboratory monitoring.5 Close monitoring of laboratory results and periodic liver biopsies are used to monitor for relapse. High-dose immunosuppression must be restarted if relapse occurs. Successful discontinuation of treatment in AIH-1 is possible in approximately 20% of patients.5 The rest of the patients, including most patients with AIH-2, require a small dose of steroids to be continued indefinitely. Azathioprine has been used as prolonged long-term monotherapy in adults; however, due to an unknown, long-term side effect profile in children, more research is needed in this area.5,27

For the children who respond well to immunosuppressive drugs, the long-term survival rate and quality of life is outstanding. However, despite treatment, the development of end-stage liver disease requiring liver transplant has been reported in 8.5% of children age 8 to 14 years after diagnosis.5

In terms of other treatment regimens, budesonide in combination with azathioprine is formally being studied for inducing and maintaining remission in adults and in children. A large multinational, randomized control trial comparing budesonide and prednisone was completed by Csepregi et al.28 that showed better disease response to treatment with budesonide plus azathioprine than prednisone plus azathioprine. However, the study results were found to be unreliable due to issues in the control group.29 Firstly, the initial prednisone dose was lower than the standard initial dose. Secondly, the prednisone dose was reduced regardless of clinical and biochemical response, which is not standard treatment practice. Further studies about the efficacy of budesonide and its use in AIH are still needed.

### TABLE 1.

#### Diagnostic Criteria for AIH in Children

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion of common causes of hepatitis in children</td>
<td>Viral hepatitis A, B, C; Wilson’s disease; alpha-1 antitrypsin deficiency; fatty liver</td>
</tr>
<tr>
<td>Elevated serum transaminases</td>
<td>&gt;Upper limit of normal for the laboratory</td>
</tr>
<tr>
<td>Elevated serum IgG</td>
<td>&gt;Upper limit of normal for age</td>
</tr>
<tr>
<td>Type 1 AIH</td>
<td>Titer ≥1:20</td>
</tr>
<tr>
<td>ANA and/or SMA</td>
<td>Titer ≥1:10</td>
</tr>
<tr>
<td>Type 2 AIH</td>
<td>Seropositive</td>
</tr>
<tr>
<td>Anti-LKM-1 and/or anti-LC-1</td>
<td></td>
</tr>
<tr>
<td>Type 1 or Type 2 AIH</td>
<td>Interface or multilobular hepatitis</td>
</tr>
<tr>
<td>Anti-SLA</td>
<td>Normal magnetic resonance or retrograde cholangiogram</td>
</tr>
<tr>
<td>Normal cholangiogram</td>
<td></td>
</tr>
</tbody>
</table>

*All of the above criteria do not have to be positive for a diagnosis of AIH. Abbreviations: AIH, autoimmune hepatitis; ANA, antinuclear antibodies; Anti-LC-1, anti-liver cytosol type 1 antibodies; LKM-1, liver kidney microsomal type 1 antibody; SLA, anti-soluble liver antigen antibody; IgG, immunoglobulin G; SMA, smooth muscle antibody. Adapted from Mieli-Vergani and Vergani.2*
This regimen may still be promising, as budesonide has a much lower side-effect profile compared to prednisone. Other immunosuppressive drugs used to treat difficult cases of AIH in children include cyclosporine, myco-phenolate mofetil, and tacrolimus.

Liver transplant is an option in patients who present with fulminant liver failure and are nonresponsive to immunosuppressive therapy. About 10% to 20% of children with AIH require a liver transplant. However, it is important to note that recurrence of AIH may occur in approximately 20% of patients after transplantation. The future of AIH treatment lies in immunotherapy, with the goals of increasing treatment safety and efficiency. It is believed that restoring T-cell regulatory function can selectively block the immune attack on the liver. These therapies are in the preliminary stages of development and it will be a while before they will be available for therapy in children.

**SUMMARY**

AIH is an immune-mediated, progressive, inflammatory liver disorder. It is a rare cause of end-stage liver disease in children. There are two types of AIH: AIH-1 is sero-positive for ANA and/or SMA, and AIH-2 is sero-positive for anti-LKM-1 and/or for anti-LC-1. In children, AIH has a more aggressive course, and initiation of early treatment is the key to remission and prevention of development of cirrhosis or liver failure. Thus, for the general pediatrician, the goal is to suspect AIH in a child when clinical signs and/or laboratory markers are apparent, refer to a specialist quickly, and make the correct diagnosis efficiently so that the immunosuppressant therapy can be initiated immediately, decreasing the occurrence of cirrhosis or liver failure.

**REFERENCES**


