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FIELD OF VISION

Diagnostic criteria for autoimmune hepatitis in children: A challenge for pediatric hepatologists

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Abstract

Autoimmune hepatitis (AIH) is a progressive inflammatory liver disorder that is rare in children and adolescents. AIH has a broad clinical spectrum and a quick response to treatment with corticosteroids and immunosuppressive medication. The available diagnosis criteria have limitations and should be evaluated in pediatric populations. Recently, some studies reported that the 2008 simplified diagnostic criteria for AIH could be used in children with high sensibility and specificity. In addition, the authors reported that globulin and immunoglobulin G levels can be used interchangeably for diagnostic purposes. They also demonstrated that the 2008 simplified criteria fail in identifying patients with fulminant hepatic failure. Here, we discuss the limitations of the use of these criteria in pediatric patients and the requirement of more studies to improve the diagnosis of AIH in children.

Key words: Child; Autoimmune hepatitis; Liver diseases; Diagnosis; Autoimmunity

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INVITED COMMENTARY ON HOT ARTICLES

Autoimmune hepatitis (AIH) is particularly aggressive in children and progresses rapidly unless immunosuppressive treatment is promptly started. The recent publication by Mileti *et al*[1] on the validation of simplified diagnostic criteria for autoimmune hepatitis in children caught our attention for its updated theme, with great relevance to pediatrics and hepatologists. We highly recommend reading the manuscript.

AIH is a progressive inflammatory liver disorder that is rare in children and adolescents. It affects patients who have lost immune tolerance to liver self-antigens[2-4]. It predominates in females, and it is serologically characterized by high levels of transaminases and immunoglobulin G (IgG) and the presence of auto-antibodies and histologically characterized by interface hepatitis in the absence of a known etiology[3]. The age of onset of AIH ranges from 6 mo to 75 years; however, it is rare

before 2 years, and the incidence is higher between 10 and 30 years[3].

The clinical spectrum is broad; asymptomatic patients may only have laboratory abnormalities. Patients may also present with clinical symptoms similar to acute viral hepatitis and even severe liver failure (acute, chronic or fulminant)[3]. Auto-antibodies, such as antinuclear antibodies (ANA), anti-smooth muscle antibody (SMA) and anti-liver/kidney microsome type 1 (anti-LKM1), are important for the diagnosis of AIH. Based on the pattern detected, AIH can be classified into two types: type 1, in which ANA and/or anti-SMA are detected, and type 2, in which anti-LKM1 is detected[5].

Some histological findings can suggest the presence of AIH: piecemeal necrosis with periportal/periseptal lymphocytic infiltrate; interface hepatitis with the destruction of hepatocytes at the periphery of the lobule and erosion of the limiting plate; hepatic regeneration with "rosette" formation; and "bridging collapse", in which connective tissue collapses and expands from the portal area into the lobule[6].

Treatment with corticosteroids and immunosuppressive agents is usually efficient in controlling AIH[3]. Prednisone alone or combined with azathioprine is the main treatment, and it is aimed at reducing liver inflammation and inducing clinical remission and better survival rates. The treatment response is characterized by clinical improvement and the reduction of aminotransferase levels to normal or up two times the highest reference value[3].

Given the necessity to standardize the diagnosis and establish early treatment, in 1993, the International Autoimmune Hepatitis Group (IAIHG) created diagnostic criteria for AIH. Those criteria were revised in 1999 to improve specificity and simplify the scoring system, as cited in the discussion section of the manuscript[1,7]. Simplified diagnostic criteria were established in 2008 to make their use in clinical practice easier.

Mileti *et al*[1] selected 37 children under 21 years old with a diagnosis of AIH and 40 children diagnosed with other liver diseases and evaluated the sensitivity and specificity of the diagnostic criteria proposed in 2008. They found a sensitivity of 87% and a specificity of 89% for the 2008 criteria and also observed that these criteria did not rank patients with signs of fulminant hepatic failure (FHF) well. The authors also compared the use of IgG and serum globulin levels to grade the criteria and concluded that they may be used interchangeably without impairing the final score.

The use of 2008 diagnostic criteria might simplify the day-to-day work of hepatologists and might provide an interesting measure for pediatric patients. Based on the cited results and considering that autoimmune hepatitis is important in the differential diagnosis of liver disease in childhood, we discuss some important points that may affect the use of these criteria.

Use of diagnostic criteria in pediatric patients

In general, the adoption of diagnostic criteria is considered to be an attempt to standardize observations and clinical procedures for different centers with the main goal of a "common language". Diagnostic criteria should contain well-defined measures and should be easy to apply in clinical practice to facilitate disease classification, diagnosis and, consequently, treatment. Another important issue concerning diagnostic criteria is the possibility of distinguishing patients who need to be assigned to different therapies or management strategies, even if the diagnosis is not clearly established. This important feature of the diagnostic criteria will certainly allow early treatment, which might improve the outcome of patients.

For many diseases and clinical conditions, we already have diagnostic criteria that were usually established for the adult population and subsequently adapted to pediatric patients. The ideal situation would be that the diagnostic criteria used for children arise from studies on this age group.

Another important point is that diagnostic criteria raise the possibility of a disease, but in most cases, it is difficult to exclude other diagnoses. For example, the diagnosis of rheumatic fever with the criteria originally proposed by Jones[8] in 1944 includes a combination of arthritis, fever, and a high sedimentation rate in the presence of a recent Group A streptococcal infection. However, many children with juvenile arthritis also present with exactly the same features[9].

For AIH, the same problem occurs, with the criteria being initially established for adults and later adopted with changes for pediatric patients. In its first version in 1993, based on consensus from the IAIHG, the diagnosis of AIH in the pediatric population was not considered to require separate diagnostic criteria, as cited by Mileti *et al*[1]. Two other studies attempted to evaluate recent criteria (1999 and the simplified criteria created in 2008) in pediatric populations, and they had controversial results. Those studies are listed and compared with the Mileti *et al*[1] study in Table 1.

The authors generally concluded that the 1999 and 2008 diagnostic criteria could be used in children with good sensitivity and specificity in most cases, but they also showed some limitations. First, in children with the final diagnosis of primary sclerosing cholangitis (PSC), the study of Ebbeson *et al*[10] found that the 1999 criteria adequately scored these patients as "not AIH", while Hiejima *et al*[11] showed that using both criteria, all 5 children with PSC were graded as having AIH. Considering these findings and the possibility of AIH/PSC overlap syndrome in children, the use of gamma-glutamyl transferase could improve the specificity of the 1999 criteria but would not improve the 2008 criteria. Therefore, the recent recommendation of performing cholangiographic evaluation in all children with an initial diagnosis of AIH was added[12,13].

The second issue is the limitation cited by Mileti *et al*[1] regarding the reliability of the 2008 criteria in identifying patients with FHF. The acuteness and severity of FHF

Table 1 Summary of pediatric studies on the validation of diagnostic criteria for autoimmune hepatitis

Authors	Place and date	*n*	Diagnostics	Tested criteria	Results	Conclusions
Mileti *et al*[1]	United States, 2012	68	37 AIH for 1999 criteria/ 31 AIH for 2008 criteria 40 non-AIH	1999 and 2008	1999 criteria: 29 of 31 subjects (94%) as definite AIH; 2 of 31 subjects (6%) as probable AIH Simplified criteria: 25 of 31 subjects (81%) as definite AIH; 2 of 31 subjects (6%) as probable AIH The 2008 diagnostic criteria had a sensitivity of 87% and a specificity of 89% and did not identify 4 patients with AIH and fulminant hepatic failure	The 2008 criteria showed high levels of sensibility and specificity Patients with fulminant hepatic failure need the 1999 criteria Globulin and immunoglobulin G can be used interchangeably
Ebbeson *et al*[10]	Canada, 2004	28	21 AIH 4 PSC 3 ASC	1999	18 of 21 (86%) with AIH scored as definite AIH and 3 of 21 (14%) scored as probable All patients with isolated PSC scored as not AIH	The IAIHG scoring system has a use in children Using the GGT ratio may improve the specificity for children
Hiejima *et al*[11]	Japan, 2011	56	20 AIH 36 non-AIH liver diseases	1999 and 2008	Sensitivity and specificity of the 1999 criteria were 100% and 81%, respectively Sensitivity and specificity of the simplified criteria were 55% and 86%, respectively All 5 children with PSC were graded as having AIH by both criteria	The specificity of the simplified AIH criteria is high Simplified criteria could not differentiate between AIH and PSC and do not seem to be a reliable diagnostic tool in children

AIH: Autoimmune hepatitis; PSC: Primary sclerosing cholangitis; ASC: Autoimmune sclerosing cholangitis; IAIHG: International autoimmune hepatitis group; GGT: Gamma-glutamyl transferase.

demand a rapid and precise diagnostic definition. If the diagnostic criteria provide information in this special situation, treatment with corticosteroids could be started promptly. Thus, further research is important to identify factors or measurements that could improve the diagnosis of FHF.

The third issue is that the auto-antibodies used for diagnosis often have lower titers in children than the cut-off values considered positive in adults and utilized in both diagnostic criteria (1999 and 2008)[4]. The reactivity of ANA, SMA and anti-LKM1 is low; therefore, titers of 1/20 for ANA and SMA and 1/10 for anti-LKM1 can be considered relevant in children[4]. The 2008 and 1999 criteria consider titers above 1/40 to be significant, and the laboratory test is performed with a minimum dilution of 1/40; therefore, children with titers of 1/20 could be false negative for the tested auto-antibody. Therefore, in children with clinical history and a physical examination compatible with AIH, we should not exclude this diagnosis when negative auto-antibody results are obtained.

The fourth issue is the use of histological findings as one point of the diagnostic criteria for AIH. Histology was included in the 1993 and 1999 criteria, and each feature of the liver biopsy was scored as a separate item[7]. In contrast, the simplified criteria utilize only two parameters: histology compatible with AIH and histology typical of AIH[14]. The concern is that a biopsy is not possible at the beginning of follow-up in many pediatric cases because these patients usually exhibit significant liver dysfunction and coagulopathy. Thus, sometimes, clinicians do not have this information and face the necessity of initiating corticosteroid therapy without knowledge of the histological condition. Björnsson *et al*[15] questioned the importance of histology in the diagnosis of typical cases of AIH and concluded that the majority of patients with typical laboratory features of AIH are likely to have compatible liver histology. Not surprisingly, liver biopsy may reveal another hepatic disease that might affect clinical management. We agree that whenever possible, liver biopsy should be performed prior to initiating immunosuppressive therapy in patients with AIH. However, we also believe that if it is not possible to obtain initial histological findings, the initiation of treatment for highly suspected patients should not be delayed. Indeed, for the majority of cases with suggestive clinical features and compatible laboratorial data, the diagnosis of AIH can be reliably established in the absence of liver histology. Ultimately, liver biopsy should be performed, whenever possible, to differentiate other hepatic diseases and according to the guidelines of the American Association for the Study of Liver Disease Practice Guidelines for Autoimmune Hepatitis[13].

The last point to be addressed is the sample size of the Mileti *et al*[1] cross-sectional study, which was composed of just a few individuals classified with both criteria. Similar to other pediatric studies on AIH, the sample size is small. Additional studies should be performed with other populations to establish the best diagnostic criteria for pediatric AIH and to address all other points that require further elucidation in AIH and hepatic-related disorders.

In conclusion, the use of 2008 diagnostic criteria is an important tool in the diagnosis of AIH in children, and the study of Mileti *et al*[1] clearly corroborates this view. However, considering the existing criteria, more studies with larger series seem to be necessary to validate their use in pediatric patients. Finally, we believe that additional pediatric studies on AIH might allow for the clear differentiation between AIH and PSC, include

alternative ways to define fulminant hepatic failure and establish lower auto-antibody titers for pediatric patients.

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