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Validation and Modification of Simplified Diagnostic Criteria for Autoimmune Hepatitis in Children

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Abstract

Background & Aims—Criteria for the diagnosis of autoimmune hepatitis (AIH) were formalized in 1993 and revised in 1999. Simplified criteria were developed in 2008, for adults only. We aimed to establish clinically useful diagnostic criteria for AIH in children by validating the 2008 criteria in a pediatric cohort.

Methods—Baseline data were available from 37 and 31 subjects with AIH (70% female) and 40 and 26 subjects without AIH (30% female), which were used to calculate the 1999 and 2008 criteria, respectively. Sensitivity and specificity of the simplified criteria were calculated using 1999 criteria as the standard for subjects with available data for both criteria.

Results—The 1999 standard designated 29/31 subjects (94%) as definite AIH and 2/31 subjects (6%) as probable AIH. The simplified criteria identified 25/31 subjects (81%) as definite AIH, 2/31 subjects (6%) as probable AIH. Only 1/5 patients with AIH who presented with fulminant hepatic failure (FHF) was identified by the simplified criteria as having AIH. The 2008 diagnostic criteria had a sensitivity of 87% and specificity of 89% (area under the receiver operating characteristic [AUROC] curve=0.98). After removing data from patients with FHF from the analysis, the sensitivity increased to 100%. Modifying the 2008 diagnostic criteria to include either level of globulin or immunoglobulin (Ig)G resulted in similar sensitivity (92%) and specificity (95%; AUROC curve=0.99) values.

Conclusions—The 2008 criteria diagnose AIH in children with high levels of sensitivity and specificity, and are easier to use in the clinic. Diagnosis of AIH in patients who present in FHF

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requires the 1999 criteria. Levels of globulin and IgG can be used interchangeably in the simplified diagnostic criteria.

Keywords

pediatric liver disease; scoring system; diagnostic; autoimmunity

INTRODUCTION

In 1993, the International Autoimmune Hepatitis Group (IAIHG) was developed a method for diagnosing autoimmune hepatitis (AIH) and differentiate it from chronic active hepatitis. The original criteria classified patients as having “definite” or “probable” AIH¹ with revisions made in 1999 to improve specificity and simplify the scoring system.² The 1999 revised original criteria reported specificity of 90%, improving the ability to distinguish AIH from other autoimmune liver diseases. The criteria remained complex, including 13 categories and 29 possible grades (Table 1 supplementary materials). This complexity made the 1999 revised original criteria challenging for clinical use.

In 2008 the IAIHG developed simplified diagnostic criteria, including only four categories: autoimmune markers, immunoglobulin G (IgG) levels, histology, and absence of viral hepatitis (Table 2 supplementary materials). This scoring system, unlike the previous two, was developed using an international cohort from 10 countries. Based on receiver operating characteristic (ROC) curves, scores of ≥ 6 had a sensitivity of 88% and specificity of 97% for diagnosing probable AIH.³ A score of ≥ 7 had a sensitivity of 81% and specificity of 99% for definite AIH.³ The 2008 criteria have been validated in other adult cohorts over the last 3 years, with similar results reported.^{4–8}

Based on consensus from the IAIHG in 1993, the diagnosis of AIH in the pediatric population was not considered to require separate diagnostic criteria. However, distinguishing AIH from primary sclerosing cholangitis (PSC) and overlap syndromes in children was a recognized problem. Two studies in the literature highlight the use of the scoring systems in the pediatric population: validating the 1999 and 2008 criteria. The first demonstrated that the earlier scoring systems could be applied in the pediatric population but noted the importance of validation in children due to differences between the pediatric and adult populations.⁹ The second study, evaluating the 2008 simplified criteria, demonstrated high specificity but low sensitivity, calling into question the utility of this criteria for use in the pediatric population.¹⁰ Prompt diagnosis of AIH is crucial for the initiation of immunosuppressive medications and substantially improves prognosis.^{11,12} Thus, using the simplified criteria would be ideal for diagnosis in children. In this study we applied the IAIHG simplified criteria to a larger pediatric cohort with AIH and other chronic liver diseases to validate its usefulness in children. Additionally we modified the simplified criteria to include the use of globulin as a surrogate for IgG.

METHODS

Study Population

All children (age less than 21 years at presentation) included in this study were from a single pediatric hepatology center at a tertiary care hospital. Children with AIH were identified through ICD-9 codes, pathology reports, and cross referencing with pediatric hepatology patient lists from 1991 to 2010. AIH subjects had to have all baseline laboratory, histology, demographic, and clinical information necessary to calculate and confirm the diagnosis of autoimmune hepatitis using the 1999 revised original scoring system. These patients also met the diagnosis of AIH using the codified descriptive criteria from 1993 and all subjects

diagnosed with AIH responded to immunosuppressive therapy. Only laboratory data from the time of initial diagnosis was used for analysis. All AIH patients were classified as Type I AIH except for one female with Type II AIH. One patient had AIH-PSC overlap. Five patients with AIH presented in fulminant hepatic failure (FHF).

All non-AIH subjects had other confirmed liver diseases and were identified from pediatric hepatology databases from 1991 to 2010. They were only included in the study if they had sufficient data available to calculate both the 1999 and 2008 scores. Diagnoses included primary sclerosing cholangitis (N=10), viral hepatitis (N=5), nonalcoholic steatohepatitis (N=12), and metabolic/genetic liver diseases (N=13: cystic fibrosis, alpha-1-antitrypsin disease, glycogen storage disease, biliary atresia, progressive familial intrahepatic cholestasis type 2 and 3, ornithine transcarbamylase deficiency, bile acid conjugation defect, methylmalonic acidemia, and congenital hepatic fibrosis). Viral hepatitis was excluded using serologies for hepatitis A, B and C. Four AIH subjects were excluded because they were initially diagnosed at other institutions and baseline data were not available for them to be included in the analysis (Figure 1). The study was approved by the University of California San Francisco Committee on Human Research.

Scoring Systems

Since the 2008 simplified criteria did not include response to therapy in the diagnostic score, we opted to use only pre-treatment criteria scores from the 1999 original revised scoring system when establishing the diagnosis of AIH. For the 1999 original revised criteria, a score of 10–15 equated to a probable AIH diagnosis and scores > 15 indicated a diagnosis of definite AIH (Table 1 supplementary materials). For the 2008 simplified criteria, a score of 6 was used for probable AIH and ≥ 7 constituted definite AIH (Table 2 supplementary materials).

The 2008 criteria were calculated using the four predefined parameters: auto-antibodies, IgG level, liver histology, and absence of viral hepatitis. To evaluate IgG compared to globulin level, the 2008 criteria were subsequently calculated using serum globulins instead of IgG. Those who had serum globulins in the normal range received 0 points, if the level was above normal the subject received 1 point and those who had 1.1 times the upper limit of normal received 2 points.

Statistical Analyses

Sensitivity and specificity of the 2008 criteria were calculated using 1999 criteria as the “gold standard.” In addition, sensitivity and specificity were calculated modifying the 2008 criteria by using either IgG or globulin levels. Kappa statistic was used to evaluate agreement between scores using IgG versus IgG or globulin levels. Receiver operating characteristic (ROC) curves were plotted to illustrate the specificity and sensitivity of the 2008 simplified diagnostic criteria compared to the 1999 revised original criteria. Results were reported as percentages, or in the case of continuous variables, median and interquartile ranges (IQR). The Mann-Whitney U-test was used to evaluate differences between two groups with continuous variables and Chi-squared test for dichotomous variables. Fisher’s exact test was used where appropriate. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed on STATA ® Version 11.1 software (College Station, TX).

RESULTS

An initial 238 subjects with various liver diseases were evaluated. We identified 77 patients (37 AIH, 40 non-AIH) who had complete data available to calculate the 1999 score (Figure

1). Within the AIH group, 31 of 37 subjects had IgG levels to calculate the 2008 score but all 37 subjects had either or both IgG or globulin levels available at diagnosis. Of these patients 36 had AIH and 1 had overlap AIH-PSC at the time of diagnosis. From the non-AIH group, 26 of 40 subjects had IgG levels to calculate the 2008 score but all 40 subjects had either or both IgG or globulin levels available at initial diagnosis. There were more females (70%) and family history of other autoimmune disease was more common in the AIH group. AIH patients had higher median serum AST, ALT, IgG, total globulin, total protein and autoantibody marker positivity (Table 1). Median serum alkaline phosphatase levels were similar between groups (Table 1).

Within the AIH group, the 1999 original revised criteria categorized 29/31 (94%) as definite AIH and 2/31 (6%) as probable AIH. The 2008 criteria defined 25/31 (81%) as definite AIH, 2/31 (6%) as probable AIH and 4/31 (13%) were not identified as AIH. All 4 of these subjects not classified as AIH according to the 2008 criteria presented in fulminant hepatic failure (FHF). All of them had acute presentations within 8 weeks of symptoms; INR levels were greater than 1.5 and not correctable with Vitamin K; significantly elevated transaminases; and hepatic encephalopathy. Three of these patients required transplantation within 2 weeks of diagnosis. One patient was listed for transplant but improved after the initiation of immunosuppressive medications.

Validation of the 2008 score using IgG levels

Sensitivity of the 2008 diagnostic criteria using IgG was 87% (95% CI: 71% – 95%) in our pediatric cohort, including patients presenting with FHF. Without the FHF subjects, the sensitivity increased to 100% (95% confidence interval 88% – 100%). Specificity of the 2008 criteria was 89% (95% CI: 71% – 96%) as some of the patients with primary sclerosing cholangitis (PSC) had scores of 6. Only 8 PSC patients had sufficient information to calculate the 2008 score. Among these, three had scores of 6 using the 2008 diagnostic criteria, categorizing them as “probable” AIH. Liver pathology revealed biliary tract changes and they had abnormal cholangiograms or magnetic resonance cholangiopancreatography. The 2008 criteria showed excellent discrimination of AIH (AUROC 0.98, Supplementary Figure 2). At a cutoff point of ≥ 6 (probably AIH diagnosis) sensitivity was 87% and a specificity was 89%; at ≥ 7 (definite AIH diagnosis), sensitivity was 80% and specificity was 100%.

Validation of the 2008 score using IgG levels or serum globulin

The 1993 original diagnostic criteria and the 1999 revised original criteria both included the option of using IgG or serum globulins but the 2008 criteria used only IgG levels in calculating a score. Due to the close correlation of IgG and serum globulins, sensitivity and specificity were also calculated using serum globulins levels when IgG levels were missing¹³. Using either IgG or globulins provided a total of 77 subjects (37 AIH and 40 non-AIH; Table 2). Sensitivity using this “modified” 2008 criteria was 92% (95% CI: 79% – 97%) and specificity was 95% (95% CI: 84% – 99%) with an AUROC of 0.99 (Supplementary Figure 3). The kappa statistic showed excellent agreement between the diagnostic scores when calculated using IgG versus using IgG or globulin (kappa = 0.8491).

There was no difference in laboratory tests or autoantibody marker positivity between those who had IgG measured and those who had serum globulin measured. When comparing only the subjects who had both IgG and serum globulin levels (N=53) we found that there were 4 subjects where scores changed when using serum globulin instead of IgG levels. One subject with PSC had a score of 6 (probable AIH) when using IgG but that score dropped to 5 (not AIH) when using serum globulin levels. The other three score changes were in AIH subjects. One of the patients presenting in FHF had a score of 5 (not AIH) when using IgG

but that score increased to 6 (probable AIH) when using serum globulin levels. Another AIH subject had a score of 7 (definite AIH) with using IgG but this dropped to a 6 (probable AIH) when using serum globulins. The last patient scored 6 (probable AIH) using IgG but increased to 8 (definite AIH) using serum globulin levels. Use of serum globulins instead of IgG thus did not change our ability to diagnose AIH. Overall the results are the same with AUROC for 2008 scoring system using IgG being 0.978 and using serum globulins 0.985.

DISCUSSION

This cross-sectional study compared the 2008 criteria for diagnosing AIH with the 1999 revised original criteria in a pediatric cohort with liver disease. We showed that the 2008 simplified criteria are useful for pediatric patients. Prior studies evaluated these criteria compared to codified descriptive criteria first developed by the IAIHG in 1993.²⁻⁶ While all of our AIH subjects met the diagnostic criteria based on the 1993 criteria, we chose to use the 1999 original revised criteria as our “gold standard” due to its established use in clinical and research settings and the validation of this criteria in the pediatric population⁹. Despite the relatively small sample size used in this study, we demonstrated excellent sensitivity and specificity of the 2008 criteria compared to the 1999 criteria consistent, with the results seen in adult studies.

We also showed that either IgG or serum globulin could be used to diagnose AIH in children. The 1993 and 1999 criteria used serum globulin and IgG levels interchangeably.^{1,2} Correlation between serum globulin levels and IgG have been previously established in patients with chronic liver disease.¹³ Hennes et al. discussed the use of IgG versus gamma globulin and found that there was a close correlation between the two (Pearson coefficient: $r = 0.87$).³ They chose to use IgG alone in their analysis due to many missing gamma globulin levels in their cohort. Missing data is frequent in many studies and this was also true of our population. For this reason, we validated the 2008 criteria using IgG levels first then using either IgG or serum globulins to determine the utility of both criteria. We found that calculating the simplified score using serum globulins was equally effective as using IgG and may be used when IgG is not available.

One limitation is that the 2008 criteria do not reliably identify patients presenting in FHF due to AIH. The 1999 criteria should be used to confirm the diagnosis of AIH in these patients. In our cohort we found that 4 out of 5 AIH patients presenting in FHF had normal IgG levels and 3 out of 5 had normal serum globulin levels. Yeoman et al also found this in an adult population and were cautious to note that both the 1999 and 2008 criteria were not developed with FHF in mind.⁵

In addition, there could be selection bias in the selection of non-AIH patients. Nearly 200 charts of non-AIH patients were reviewed to find sufficient that included all the required data to calculate 1999 and 2008 scores. These patients may have differed from those not included in that they had a more extensive evaluation than those with more readily diagnosed non-AIH disease.

Another concern is that of diagnosing children with other autoimmune liver diseases. Due to the retrospective nature of our study, we recognize that our study likely did not identify all the patients with autoimmune sclerosing cholangitis at diagnosis. We identified only one subject who presented with an AIH/PSC overlap syndrome. Gregorio et al found that 50% of patients with characteristics diagnostic of AIH actually had bile duct disease at presentation, diagnosed by cholangiography.¹⁴ Diagnostic guidelines from the American Association of the Study of Liver Diseases now include the need for cholangiographic evaluation in children at the time of diagnosis.^{15,16} We reviewed all available cholangiograms that were

subsequently performed on our AIH patients and all 8 yielded normal results with no bile duct abnormalities. In our cohort 3 out of 8 subjects with PSC were diagnosed with “probably AIH” using the 2008 simplified criteria. All of the PSC patients had biliary tract changes on their pathology and abnormal cholangiograms or magnetic resonance cholangiopancreatography indicative of PSC. While a score of 6 inaccurately diagnoses these patients as having “probable AIH” and decreases the specificity of the 2008 criteria, the clinical diagnosis and management should be guided by the biopsy results and not the score alone. Ebbeson suggested that replacing alkaline phosphatase ratio with GGT ratio in the IAIHG score may identify better those children with biliary disease⁹. Studies evaluating the IAIHG scoring systems in patients with PSC and overlap syndromes show that the revised original criteria and the simplified criteria have similar specificity in these patients.^{17–19}

In conclusion, the 2008 diagnostic criteria for AIH have excellent sensitivity and specificity when used in a pediatric cohort, except in those AIH patients with FHF. Since there are only 4 variables to consider in the calculation of the 2008 diagnostic criteria, it is easier to use in a clinical setting compared with the 1999 system. However, cholangiographic studies should be performed in all children with AIH to exclude PSC.¹⁶ Serum globulin levels and IgG can be used interchangeably and can be used when IgG levels have not been obtained. The sensitivity and specificity in our pediatric cohort were similar to what has been reported in the adult population.

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Abbreviations

AIH	autoimmune hepatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
ANA	antinuclear antibody
AST	aspartate aminotransferase
AUROC	area under receiver operating characteristic curve
CI	confidence interval
FHF	fulminant hepatic failure
GGT	γ -glutamyltranspeptidase
IAIHG	International Autoimmune Hepatitis Group
IgG	immunoglobulin G
IQR	interquartile range
LKM	liver-kidney-microsomal
NASH	non-alcoholic steatohepatitis
PSC	primary sclerosing cholangitis
ROC	receiver operating characteristic

SLA	soluble liver antigen
SMA	smooth muscle antibody

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Figure 1.

Flow diagram of the initial 238 subjects evaluated for inclusion in this study; 77 patients (37 AIH, 40 non-AIH) had complete laboratory, histologic, demographic and clinical data available to calculate the 1999 AIH score.

Table 1

Baseline characteristics of AIH and non-AIH subjects

Characteristics	AIH	Non-AIH*	P-values
Number of subjects, N (%)	37 (58.1)	40 (51.9)	
Median Age (range, in years)	13 (1–19)	10 (0.1–19)	0.0154
Gender, N (%)			
Female	26 (70.3)	11 (29.7)	<0.0001
Ethnicity, N (%)			<0.0001
White	22 (59.5)	14 (35.0)	
Black	7 (18.9)	1 (2.5)	
Latino	5 (13.5)	16 (40.0)	
Asian	1 (2.7)	6 (15.0)	
Other/Missing	2 (5.4)	3 (7.5)	
Laboratory Markers, median (IQR)			
AST, IU/L	709 (265, 2350)	80 (41, 206)	<0.0001
ALT, IU/L	440 (265, 1701)	97 (46, 257)	<0.0001
ALP, U/L	240 (179, 590)	258 (159, 715)	0.943
IgG, mg/dL (N=57)	2430 (1793, 4260)	1170 (845, 1880)	<0.0001
Globulin, g/dL (N=73)	4.6 (3.9, 5.7)	3 (2.7, 3.4)	<0.0001
Albumin, g/dL	3.3 (2.5, 4.1)	4.1 (3.8, 4.5)	<0.0001
Total protein, g/dL	7.9 (7.1, 9.3)	7.2 (6.6, 8)	0.0011
Autoantibody positive (%) [^]	37 (100)	19 (47.5)	<0.0001
Other autoimmune disease [‡] (%)	10 (27)	3 (7.5)	0.023

* Non-AIH = PSC (10), NASH (12), viral hepatitis (5), metabolic liver disease (13)

[^] Autoantibodies in AIH and non-AIH were ANA 92% and 17.5%; SMA 72% and 52%; LKM 3% and 0 respectively. ANA and SMA were positive in 30% and 57% of PSC patients respectively.

[‡] Other autoimmune disease in either patient or first degree relative.

Table 2
Comparison of 1999, 2008 and modified 2008 Diagnostic Scoring Criteria for Autoimmune Hepatitis in Children

Diagnosis (n=57)	AST IU/L	ALP:AST Ratio	Autoantibodies (%)	IgG mg/dL	1999 Score (N=77)	2008 Score (N=57)	Modified 2008 score* (N=77)
Median (IQR)				Median (range)			
AIH (31)	743 (265, 1549)	0.37 (0.18, 1.07)	31 (100)	2430 (1793, 3575)	18 (13, 23)	8 (5, 8)	8 (5, 8)
AIH, non-FHF	789 (262, 1443)	0.43 (0.18, 1.07)	26 (100)	2860 (2243, 3700)	19 (15, 23)	8 (6, 8)	8 (6, 8)
AIH, FHF	667 (331, 2511)	0.31 (0.19, 0.56)	5 (100)	1490 (1120, 1740)	17 (13, 18)	5 (5, 7)	5 (5, 7)
Non-AIH (26)	86 (52, 174)	4.06 (2.48, 5.05)	13 (50)	1170 (845, 1640)	4 (-1, 11)	3 (0, 6)	3 (0, 6)
PSC (8)	88 (66, 133)	4.33 (3.3, 5.36)	4 (50)	1770 (1420, 2025)	5 (-1, 11)	4 (2, 6)	4 (2, 6)
Metabolic liver disease (13)	109 (41, 181)	4.01 (2.48, 5.06)	6 (46)	1140 (468, 1240)	3 (-1, 6)	3 (2, 4)	3 (2, 4)
NASH (3)	73 (30, 147)	3.9 (1.35, 5)	3 (100)	914 (794, 1240)	7 (5, 9)	3 (3, 4)	3 (2, 4)
Viral hepatitis (2)	75 (60, 89)	3.13 (2.17, 4.1)	0 (0)	1043 (965, 1120)	2 (1, 2)	1 (0, 2)	0 (0, 2)

* Modified 2008 score calculated using IgG or serum globulin.