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The Predictive Value of Autoantibodies in Determining Autoimmune Hepatitis (AIH) Severity

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Abstract

Background: The presence of autoantibodies is a prerequisite for the diagnosis of autoimmune hepatitis (AIH). However, most autoantibodies are not disease-specific, and serological overlap between AIH and other chronic liver diseases is common. Since the prognostic parameters of AIH are limited, this study aimed to investigate the relationship between histopathological findings on liver biopsy with different types of autoantibodies associated with AIH and how autoantibodies can predict the severity and extent of disease.

Methods: The present study was performed on 30 patients with a definite diagnosis of AIH according to the International Autoimmune Hepatitis Group (IAIHG) criteria. Pediatric AIH patients underwent liver tissue examinations at the time of diagnosis at accession, which confirmed characteristic histological changes. AIH-related serologic major and minor autoantibodies were measured using indirect immunofluorescence assays and ELISA kit (EUROIMMUN, Germany), respectively, and were compared within all patients, and the results were recorded. Finally, the obtained data were analyzed using SPSS V25 software.

Results: Out of 30 patients, 17 (56.66%) were female, and the age range of patients was 17-11 years (8.46 ± 6.95). Anti-nuclear antibody (ANA) (73.3%), smooth muscle antibody (SMA)-anti-smooth muscle actin antibody (ASMA) (70%), perinuclear anti-neutrophilic cytoplasmic antibodies (p-ANCA) (63%), and liver kidney microsomal (LKM) (43.3%) were the most common autoantibodies found in children with AIH. There was a significant relation between the severity of histological findings and the presence of LKM antibodies ($P < 0.05$). The highest sensitivity for predicting severe AIH based on histopathological findings was ANA autoantibody positivity and the presence of at least two primary autoantibodies (LKM and SMA-ASMA). On the other hand, positive LKM antibodies had the highest specificity and positive predictive value (PPV) in AIH severity prediction.

Conclusion: The results of the present study suggested that there might be a significant correlation between the presence of primary LKM autoantibodies and biopsy results, so it can possibly act as an accurate autoantibody for predicting the severity of AIH, while other AIH-related autoantibodies did not seem to have a significant correlation with biochemical and histological findings.

Keywords: Autoimmune hepatitis, Autoantibody, Serology, Histology, Children

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Introduction

An autoantibody can serve as a diagnostic biomarker, predict disease risk, predict treatment response, or provide insight into disease outcome. Moreover, autoantibodies played a vital role in the definition of autoimmune hepatitis (AIH) in the development of diagnostic algorithms and scoring systems, and in identifying targeted autoantigens. Despite this, autoantibodies have proved inadequate for monitoring treatment response or individualizing therapy. A conventional serological marker of AIH is anti-smooth muscle antibodies (ASMA), antinuclear antibodies (ANA), and antibodies to liver microsome type 1 (anti-LKM-1), whereas antibodies to mitochondria (AMA) are serological markers of primary biliary cirrhosis (PBC). To determine the correct classification, other clinical findings are necessary for addition to these serological features. Multiple liver diseases have been reported to produce ASMA and ANA, including acute and chronic viral hepatitis, alcoholic liver disease, PBC, and primary sclerosing cholangitis (PSC). Patients with chronic hepatitis C have tested positive for antibodies to LKM1, and patients with acute hepatitis and classical AIH have tested positive for antibodies to AMA (1).

AIH is an autoimmune disease in which the body's immune system attacks the liver cells and causes hepatic inflammation. This disease can be completely

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asymptomatic or with nonspecific symptoms such as fatigue, lethargy, weight loss, pain, anorexia, nausea, jaundice, and arthralgia of minor joints or develops into chronic liver conditions such as cirrhosis (2,3). Abnormal presentation of major histocompatibility complex II (MHC II) antigens to the surface of liver cells, possibly due to genetic predisposition or acute liver infections, induces an immune response (4). AIH has all the hallmarks of autoimmune diseases, including genetic predisposition, association with other autoimmune diseases, spontaneous fluctuations, autoantibodies, autoreactive T-cells, and immune response suppression, yet the cause is not fully understood (5). There is no clear pathognomonic pattern for the diagnosis of AIH; instead, this disorder is diagnosed based on clinical, laboratory, and histological results, which also determine the precise function of other liver disease causes (6). Histologically, the primary lesions that make up the histopathological appearance of chronic AIH are spotty necrosis, port space inflammation, interface hepatitis, Rosetta formation, emperipolesis, fibrosis, parenchymal regeneration, and cirrhosis. The presence of the above-said findings in liver biopsy is considered typical AIH. However, it should be borne in mind that these findings may be observed in other cases of hepatitis, and histology alone is not diagnostic (7,8). However, since most patients with features of AIH have compatible liver histology findings and only a small number of patients have abnormal histological findings, some studies have suggested that liver biopsies may not be required in patients with other AIH criteria (9). Liver autoantibodies are essential for the correct diagnosis and classification of autoimmune diseases of the liver, including AIH I and II, PBC, and various types of sclerosing cholangitis (10). In fact, autoantibodies are a hallmark of AIH disease and play an essential role in diagnosis.

Meanwhile, most autoantibodies are not disease-specific, and serological overlap between AIH and other chronic liver diseases is common. For instance, SMA and ANA are present in other liver diseases, including acute and chronic viral hepatitis, alcoholic hepatitis, and non-alcoholic fatty liver disease. In addition, LKM1 and AMA are common in chronic hepatitis C and acute hepatitis (11). However, like histology, the presence of autoantibodies is a prerequisite for diagnosing AIH (5,11,12). Because the prognostic parameters of AIH are limited, the aim of this study was to investigate the relationship between histopathologic findings and autoantibodies associated with AIH, as well as evaluate the predictive value of these antibodies for disease severity.

Material and Methods

This retrospective cross-sectional (descriptive-analytical) study was performed in the Pediatric Gastroenterology Clinic of Amir-Al-Momenin hospital in Zabol, Sistan and Baluchestan province, Iran. Children with definite diagnoses of AIH (between 2015-2018) were eligible for inclusion in the study in accordance with codified international criteria for AIH diagnosis. Overall, 30 pediatric patients with approved AIH according to the International Autoimmune Hepatitis Group (IAIHG) scoring system and patients who met the criteria for a definite diagnosis of AIH were included in the study (8,13).

A comparison of age, weight, family history of liver disease, and liver biochemical findings with liver histological findings is shown in Table 1. Patients' age ranged from 1 to 17 years. Asymptomatic patients with AST levels less than three times the average level were excluded. Patients with bile duct obstruction, previous treatment with immunosuppressive drugs or corticosteroids, inactive cirrhosis, presence of a hepatic lesion, positive viral markers, and markers of other chronic liver diseases were excluded from the study, as well. Demographic and clinical features from the time of presentation were collected, including age, sex, weight, laboratory investigations [albumin, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), anti-nuclear antibody (ANA), liver kidney microsomal type 1 antibody (LKM-1), anti-smooth muscle antibody (ASMA), soluble liver antigen-antibody (SLA)], and liver biopsy results. Liver biopsies of pediatric AIH patients were performed at the time of diagnosis. All had serological findings consistent with AIH and underwent liver tissue examinations at accession, which confirmed characteristic histological changes. Based on the results of the IAIHG scoring system, patients were divided into two groups: high grade (≥ 8) and low grade (<8). Measurement of autoantibodies was performed at the time of diagnosis by an indirect immunofluorescence kit (EUROMIMMUN, Germany) for primary autoantibodies (ANA, ASMA, LKM), and EUROPattern microscope was used to analyze them (EUROIMMUN, Germany), and minor autoantibodies were measured using ELISA kit (EUROIMMUN, Germany). According to the manufacturer's instructions, serum samples were tittered up to 1/320, and titers of > 1:20 and >1:40 were considered positive for anti-LKM1 and anti-SMA, respectively. HITACHI 7600 autoanalyzer (HITACHI, Japan) was used to measure the hepatic biochemical indexes.

Statistical analysis

The correlation between categorical variables was estimated using the Spearmen correlation coefficient. All statistical actions were performed using SPSS software version 25. Age, weight, liver enzyme, and other demographic information were expressed as mean ± standard deviation. The chi-square test and Student's *t* test were used to compare categorical data.

Table 1. Demographic clinical characteristics and laboratory data of 30 children with autoimmune hepatitis

Variables	AIH		All	*P* value
	High grade (≥8)	Low grade (<8)		
Number of patients (%)	16	14	30 (100%)	
Age (M) Range	7.87±5.30	9.14±4.62	8.46±4.95 1-17	0.492
Weight (kg) Range	20.48±8.90	24.85±10.34	22.52±9.69 8.7-45	0.223
Family history of autoimmune disorders (%)	10 (62.5%)	5 (35.71%)	15 (100%)	
Median total serum bilirubin (mg/dL) Range	3.77±2.62	7.26±17.833	5.4±12.21 0.2-69	0.423
Median serum alanine aminotransferase (U/L) Range	538.50±679.08	610.92±873.58	572.3±762.8 23-3276	0.951
Median serum aspartate aminotransferase (U/L) Range	696.81±984.09	578.85±661.84	641.7±815.4 31-3680	0.822
Median serum alkaline phosphatases (IU/L) Range	752.17±736.99	639.04±227.93	697.5±546.8 74-3060	0.780
Median serum albumin (g/L) Range	5.34±5.35	6.50±8.56	5.88±6.9 1.8-35	0.759

The significance level was set at $P<0.05$. The prognostic value was expressed as the corresponding 95% confidence interval (CI).

According to the frequencies of a positive antibody in patients designated with AIH, sensitivity, specificity, positive predictive value (PPV), and negative predictive value were calculated for the serological markers (gold standard).

The sensitivity of this test was determined by dividing the number of antibodies detected in AIH (true positives) by the total number of true positives plus the number of times the antibody was absent in AIH (false negatives).

In this definition, specificity is defined as the frequency of the antibody not being detected in other chronic liver diseases (true negatives) divided by the sum of the true negatives plus the frequency of the antibody being detected in other chronic liver diseases (false positives).

The accuracy of a study is defined as the number of true positives and true negatives divided by the total sample size. Positive predictability is the ratio of true positives to true positives divided by the sum of true positives and false positives. In contrast, negative predictability is the ratio of true negatives to true negatives divided by the sum of true negatives and false negatives.

A likelihood ratio (LR) is a measure of the likelihood that a test result will be accurate in diseased subjects (sensitivity) or non-diseased subjects (1-specificity)

Results

Of the 30 patients with AIH in the age range of 1-17 years, 56.66% (17 patients) were female. The mean age of the patients was 8.46±6.95 years. Diagnostic criteria of confirmed AIH were met in all children. In this study, 50% of the patients had a family history of liver and inflammatory diseases (rheumatoid arthritis, IBD) and autoimmune diseases (AIH, hypothyroidism, and celiac disease). In 73.3% of children with AIH, ANA autoantibody was observed, also, in 70% of them, SMA-ASMA autoantibody was found, and 43.3% of patients had LKM autoantibody. The highest frequency among the autoantibodies in this disease was related to perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA), which was present in about 63% of participants. The frequency of AIH-related autoantibodies in patients studied is shown in Table 2. Half of the low-grade patients and 62.5% of high-grade patients were female, but no significant difference was observed in gender distribution between the two groups ($P=0.491$). In this study, a more significant number of female patients were found, and a higher percentage of diseases were found in this group, probably because the distribution between the sexes was not significantly different.

Also, in this study, the mean age and weight of patients with different liver biopsy degrees were not significantly different. Patients with different severities of disease did not differ significantly in mean liver enzymes and family history of various liver diseases such as autoimmune and inflammatory diseases.

Comparing the patients with different histological intensities in liver biopsy in primary and ancillary autoantibodies showed that only the LKM antibody was significantly higher in high-grade patients compared to low-grade patients.

Also, having at least two primary autoantibodies (ANA or LKM, or ASMA) was considerably higher in high-grade patients than in low-grade patients. Other autoantibodies were not significantly different between the two groups (Table 3). In the studied patients, biochemical evidence of liver was compared between patients with and without significant autoantibodies. It was found that patients with and without any of the ANA antibodies, LKM, and SMA-ASMA were not significantly different in

Table 2. Autoantibodies in autoimmune hepatitis

Autoantibody		No.	%
Main autoantibody			
ANA	Positive	22	73.3
	Negative	8	26.7
LKM	Positive	13	43.3
	Negative	17	56.7
SMA-ASMA	Positive	21	70
	Negative	9	30
Others autoantibody			
SLA		1	3
AMA		6	20
p-ANNA		1	3
LP		1	3
LC-1		9	30
p-ANCA		19	63

Abbreviations: ANA, anti-nuclear antibody; ANNA, antineutrophil nuclear antibodies; SMA, smooth muscle antibody; ASMA, anti-smooth muscle actin antibody; LKM, liver kidney microsomal; p-ANCA, perinuclear anti-neutrophilic cytoplasmic antibodies; SLA, soluble liver antigen-antibody; AMA, antibodies to mitochondria, ANNA, antineutrophil nuclear antibodies; LP, liver-pancreas antibodies; Anti-LC1, anti-liver cytosol antibody Type 1.

Table 3. Autoantibodies frequency based on biopsy results

Autoantibody		Liver biopsy		*P* value
		High grade (≥8)	Low grade (<8)	
ANA	Positive	14 (87.5)	8 (57.14)	0.101
	Negative	2 (12.5)	6 (42.86)	
LKM	Positive	10 (62.5)	3 (21.43)	0.024
	Negative	6 (37.5)	11 (78.57)	
ASMA	Positive	11 (68.75)	10 (71.43)	>0.99
	Negative	5 (31.25)	4 (28.57)	
At least two main antibodies	Positive	15 (93.75)	7 (50)	0.007
	Negative	1 (6.25)	7 (50)	
SLA	Positive	0 (0)	1 (7.14)	0.467
	Negative	16 (100)	13 (92.86)	
AMA	Positive	5 (31.25)	1 (7.14)	0.175
	Negative	11 (68.75)	13 (92.86)	
p-ANNA	Positive	0 (0)	1 (7.14)	0.467
	Negative	16 (100)	13 (92.86)	
LP	Positive	0 (0)	1 (7.14)	0.467
	Negative	16 (100)	13 (92.86)	
LC-1	Positive	7 (43.75)	2 (14.29)	0.118
	Negative	9 (56.25)	12 (85.71)	
p-ANCA	Positive	11 (68.75)	8 (57.14)	0.51
	Negative	5 (31.25)	6 (42.86)	

Data are expressed as No. (%).
Abbreviations: ANA, anti-nuclear antibody; SMA, smooth muscle antibody; ASMA, anti-smooth muscle actin antibody; LKM, liver kidney microsomal; p-ANCA, perinuclear anti-neutrophilic cytoplasmic antibodies; SLA, soluble liver antigen-antibody; AMA, antibodies to mitochondria; ANNA, antineutrophil nuclear antibodies; LP, liver-pancreas antibodies; Anti-LC1, anti-liver cytosol antibody Type 1.

the concentration of liver enzymes in serum (Table 4). ANA autoantibodies and the positivity of at least two significant autoantibodies had the highest sensitivity, and positive LKM autoantibodies had the highest specificity for predicting severe AIH based on histological findings.

In contrast, ASMA autoantibodies showed the lowest sensitivity and specificity. LKM autoantibodies also had the highest PPV among autoantibodies; fewer false positive LKM autoantibody results and a higher likelihood ratio make it the optimal test for predicting and detecting severe AIH compared to other autoantibodies. The sensitivity, specificity, PPV, and negative predictive value of the primary autoantibodies in the diagnosis of AIH are shown in Table 5.

Discussion

Detection of conventional autoantibodies in unconventional settings has been a part of the overlap syndromes of AIH. Due to the non-specificity and non-pathogenicity of conventional autoantibodies, serological overlap may lead to misdiagnosis and falsely create or enhance separate disease categories. In conjunction with clinical and histological features of another disease, the presence of an autoantibody with a particular clinical association may indicate a disease overlap. However, the overlap designation requires other clinical features or pathological manifestations that indicate the disease overlap's hybridity.

When conventional autoantibodies are used to diagnose AIH and to quantify their occurrence in other chronic liver diseases, the proclivity for declaring overlap syndrome can, in part, be modulated. The serum levels of ANA, SMA, and anti-LKM1 have been regarded as diagnostically significant in AIH, as the original revised diagnostic scoring systems and simplified diagnostic scoring systems promulgated by the IAIHG grade these titers.

The diagnostic impact of individual serological markers at presentation and the magnitude of their expression remain unclear, as do the clinical implications of multiple concurrent autoantibodies at presentation. Multiple serological manifestations may be more diagnostically crucial than one single marker rather than their individual identity.

In this study, the relationship between autoantibodies and liver biopsy findings in children with AIH was investigated. For this purpose, all patients were divided into two groups, high-grade (≥8) and low-grade (<8), according to the IAIHG simplified scoring system for AIH. The main and ancillary autoantibodies related to AIH were also measured and compared. Besides, all biopsy specimens were evaluated by a hepatologist according to IAIHG criteria, and AIH ≥7 was considered to confirm the diagnosis of AIH. Age, weight, family history of liver disease, and biochemical abnormalities

Table 4. Liver tests of patients with autoimmune hepatitis based on the presence or absence of main autoantibodies

Lab test	ANA			LKM			SMA-ASMA		
	(-)	(+)	*P* value	(-)	(+)	*P* value	(-)	(+)	*P* value
AST	651.87±789.49	638.09±842.82	0.80	755.11±995.80	493.53±492.58	0.71	469.88±474.03	715.42±924.77	0.62
ALT	713.50±1106.35	520.95±620.74	0.47	694.58±936.0	412.38±435.19	0.59	441.66±477.25	628.28±861.27	0.75
ALP	755.12±136.35	675.62±640.53	0.09	768.29±632.94	597.35±399.65	0.58	635.70±463.38	721.12±584.25	0.98
Bili	1.983±1.32	6.64±14.12	0.06	7.25±16.07	2.97±2.24	0.45	10.05±22.16	3.40±2.43	0.92
Alb	3.150±0.995	6.877±7.88	0.21	6.57±7.82	4.97±5.73	0.26	7.45±6.66	5.20±7.09	0.20

Abbreviations: Alb, albumin; Bili, bilirubin, ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle actin antibody; LKM, liver kidney microsomal.

Table 5. Accuracy of autoantibodies in predicting and diagnosing autoimmune hepatitis

Antibody	Sensitivity	Specificity	PPV	NPV	LR
ANA	87.5	42.9	63.6	75	1.5
LKM	62.5	78.6	76.9	64.7	2.9
ASMA	68.7	28.6	52.4	44.4	1
At least two main antibodies	93.7	50	68.2	87.5	1.9

Abbreviations: PPV, positive predictive value; NPV, Negative predictive value; LR, Likelihood ratio; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle actin antibody; LKM, liver kidney microsomal.

with AIH histology results at the time of diagnosis were not significantly different, according to the study's findings. There is ample evidence showing that, similar to other autoimmune diseases, the pathogenesis of AIH is unrelated to the presence of most specific autoantibodies, as in the case of 10-20% of AIHs, which are classified as autoantibody-negative AIHs due to the absence of associated autoantibodies (anti-LKM, ASMA, ANA, and AMA).

Many studies show that most AIH-related autoantibodies have low disease specificity; thus, liver autoantibodies can be clearly found even in healthy people or patients with acute or chronic hepatitis with non-AIH causes. Besides, about 10-15% of AIH patients have no known autoantibodies (seronegative AIH), or these autoantibodies are found after the disease's acute stage. However, the role of autoantibodies in the pathogenesis of AIH is not fully understood (12). In the present study, ANA (73.3%), SMA-ASMA (70%), (63%) p-ANCA (63%), and LKM (43.3%) were the most common autoantibodies found among children with AIH. However, it was observed that there was a significant relationship between LKM autoantibody and biopsy results, so LKM positivity was more observed in people with higher grades in the biopsy. However, having at least two main autoantibodies could differentiate high-grade disease from low-grade when evaluated with histological findings. There was no significant difference between other autoantibodies in the two groups. Among the main autoantibodies studied, ANA positivity and the positivity of at least two main autoantibodies had the highest sensitivity, and LKM positivity had the highest potential for predicting severe AIH based on histological findings. ASMA autoantibody showed the lowest sensitivity and specificity. Less false-positive results in the LKM autoantibody test and a higher likelihood ratio, compared to other autoantibodies, make it the optimal test, especially for predicting and detecting severe AIH. In their study, Couto et al. showed that only ASMA and AAA autoantibodies were significantly associated with both biochemical and histological features of disease activity in a way that persistent high ASMA and/or AAA titers in both pediatric and adult patients with AIH were related to disease activity (14). In a study of 19 pediatric patients with AIH, Gregorio et al. found that ASMA and anti-LKM1 titers were related to biochemical evidence of disease activity. However, in this study, histological indices of disease activity had no association with the types and levels of autoantibodies studied (15). Meanwhile, this study was performed in a larger group of patients with AIH I and II. The results showed an association between LKM autoantibody and histological findings of AIH. Studies have shown that some autoantibodies are associated with disease severity in AIH patients, but there is no strong evidence for autoantibodies' spontaneous pathogenicity. However, although there is no substantial evidence that autoantibodies are pathogenic, autoantibodies are likely to be more than clinical markers and contribute at least to some extent to chronic inflammation of the liver. Therefore, in addition to liver biopsy and serum markers, screening of specific autoantibodies for autoimmune liver disease is necessary because liver autoantigen-specific antibodies may be involved in the disease's pathogenesis (16). As the major autoantigen in AIH II is Cyp2D6, if MHC I or II present it adequately, the Cyp2D6 molecule is well known by CD4 and CD8 T cells, increasing INF-y production and cytotoxicity. Evidence suggests that these events were more immunosuppressive at the time

of diagnosis than after the initiation of treatment, so the frequency of Cyp2D6-specific CD8 T cells was directly related to disease severity (16,17). Although in patients with AIH II, abnormal expression of Cyp2D6 has been suggested as an anti-LKM autoantigen at the hepatocyte level, many theories have been put forward about how other autoantibodies target intracellular antigens. Damage to hepatocytes, followed by the release of nuclear or cytosolic antigens, is one of the proposed mechanisms. However, almost all of the antigens used by AIH-related autoantibodies are not exclusively expressed in the liver but rather are expressed in various organs (12,18,19). ANA and SMA seropositivities are associated with histological findings from hepatocellular inflammation. However, these autoantibodies had low specificity in this field and cannot be used as predictable criteria. In general, type 1 autoantibodies were not associated with disease activity, which may indicate a genetic predisposition to an immune disease that has not yet been stimulated. ANA or ASMA autoantibodies are not associated with the clinical or histological severity of AIH, and histological findings are not affected by these antibodies, so the status of autoantibodies cannot be used to predict the activity or outcome of AIH disease (20-22). In the present study, ANA and/or ASMA autoantibodies were not significantly correlated with the biochemical and histological findings of AIH, and due to their low specificity, they were unreliable criteria for predicting AIH. This study was limited by the low number of participants as well as the lack of a control group. To use autoantibodies as predictors of AIH severity, further studies with a larger population of patients are needed.

Conclusion

The results of the present study suggested that there might be a significant correlation between the presence of primary LKM autoantibodies and biopsy results, so it can possibly act as an accurate autoantibody for predicting the severity of AIH, while other AIH-related autoantibodies did not seem to have a significant correlation with biochemical and histological findings.

Authors' Contribution

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Competing Interests

The authors declared that there is no conflict of interest.

Ethical Approval

This manuscript has been approved by the Ethical Committee of Zabol University of Medical Sciences (Ethics No. IR.ZBMU.REC.1397.209).

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