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Evaluating Clinical Presentations and Diagnostic Procedures in Pediatric Autoimmune Hepatitis

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Abstract

Background: The aim of the current research was to assess the clinical manifestations and diagnostic methods used in juvenile cases of Autoimmune Hepatitis (AIH).

Methods: This study employed a retrospective cross-sectional design to investigate pediatric patients diagnosed with AIH at Children's Medical Center Hospital, which is affiliated to Tehran University of Medical Sciences (TUMS), Tehran, Iran. The study included patients who received routine examinations, treatments, and follow-ups during the period from 2018 to 2021.

Results: The present investigation encompassed the evaluation of 52 pediatric patients, mostly female, with a mean age of 7.76 years. The vast majority of patients have encountered the occurrence of acute AIH. Positive findings for the Anti-Smooth Muscle Antibodies (ASMA) test were seen in 50% of the patients. The mean score for fibrosis in the observed individuals was 2.56, whereas the mean value for the Hepatitis Activity Index (HAI) in a subset of 29 patients was found to be 7.34. One patient succumbed to the condition, one case underwent transplantation, and another individual was identified as a candidate for liver transplantation.

Conclusion: Patients with AIH saw a decrease in long-term survival. There was no observed disparity in prognosis based on gender; nevertheless, it was noted that males had a shorter lifespan, perhaps attributable to an earlier beginning of the illness. The presence of cirrhosis at the time of diagnosis constituted a significant risk factor for unfavorable prognosis, as it was associated with an elevated overall risk of mortality owing to liver dysfunction.

Keywords: Autoimmune hepatitis, Child, Liver transplantation, MUSK protein, Human

Introduction

Autoimmune Hepatitis (AIH) is a chronic condition characterized by persistent inflammation and necrosis of the liver, the cause of which remains unexplained. In this context, the progression of fibrosis has the potential to lead to the development of cirrhosis. Additionally, serum autoimmune indicators include autoantibodies targeting specific and nonspecific liver antigens, accompanied by elevated levels of IgG. This syndrome often coexists with other autoimmune disorders, and it is crucial to ascertain that AIH is not triggered by persistent viral infections, alcohol use, or exposure to hepatotoxic drugs or chemicals.

It is recommended that clinicians identify AIH in all patients presenting with acute hepatitis or Chronic Liver Disease (CLD), as indicated by the presence of a newly developed coagulation issue and hepatic encephalopathy. In the context of patient care, the foremost objective is to conduct serum autoantibody measures, serum protein electrophoresis, and quantitative serum immunoglobulin testing. In some cases, the use of immediate liver biopsy and Transjugular Liver Biopsy (TJLB) might be beneficial in substantiating the clinical suspicion of acute AIH.

The prompt use of high-dose corticosteroids has the potential to effectively save the lives of some individuals who are at risk of developing CLD or progressing to cirrhosis as a result of AIH. Immunosuppressive therapies have shown the potential to provide full restoration of health in some patient populations. It is essential to exercise caution while dealing with patients affected by CLD, as their condition requires specialized treatment. Furthermore, the transfer of such individuals to secondary care institutions for emergency liver transplantation necessitates the provision of specific services. The objective of this research was to evaluate the clinical manifestations and diagnostic methods used in the diagnosis of AIH in pediatric patients. Gaining a comprehensive grasp of this condition is beneficial for this objective.

The global prevalence of AIH has been shown to be 17.44 cases per 100,000 persons. The annual prevalence of juvenile AIH in the United States is reported to be 0.4 cases per 100,000 persons. In Argentina, the incidence is somewhat higher at 0.56 cases per 100,000, while in Canada, it is lower at 0.23 instances per 100,000. Moreover, type 1 AIH is shown to be more prevalent than type 2 AIH in both populations. The precise prevalence of autoimmune hepatitis in Iran remains uncertain; nevertheless, research indicates that it is the fourth leading etiology of cirrhosis among children in southern Iran, accounting for around 11.3% of the cases.

Based on the findings of those previous studies, it may be posited that the incidence of AIH is comparatively seldom, hence accounting for the limited sample size in our study. Further publication of evidence is necessary in order to get more precise and reliable outcomes.

Materials and Methods

The present study is a retrospective cross-sectional investigation that encompassed all pediatric patients diagnosed with AIH at Children's Medical Center Hospital, which is affiliated to Tehran University of Medical Sciences (TUMS), Tehran, Iran. The study period spanned from 2018 to 2021, during which the patients received regular examinations, treatments, and follow-up care. All the pertinent data pertaining to the illness, including diagnostic evaluations, laboratory analyses, radiographic observations, and prescribed therapeutic protocols, were readily available. The primary parameters used for the diagnosis of AIH were established by using a scoring system that incorporates assessments of clinical exams, laboratory tests, and histological observations. The primary requirements are outlined in figure 1 (1).

Autoantibody[a]	
Anti-nuclear antibody or anti-smooth muscle antibody ≥1:40	1
Anti-nuclear antibody or smooth muscle antibody ≥1:80	2
Liver–kidney microsomal antibody ≥1:40	2
Anti-soluble liver antigen positive	2
Total serum IgG	
>ULN	1
≥1.1× ULN	2
Liver histology	
Compatible with autoimmune hepatitis: lymphocytic infiltrates, chronic hepatitis	1
Typical of autoimmune hepatitis:[b] interface hepatitis (portal tract lymphocytes and plasma cells infiltrating into parenchyma); emperipolesis;[c] hepatic rosette formation	2
Viral hepatitis absent	2
Pretreatment overall score	
Definite diagnosis	≥7
Probable diagnosis	≥6

ULN, upper limit of normal.
[a] Addition of points for all autoantibodies, maximum 2 points.
[b] Must have all three features to be considered "typical."
[c] Emperipolesis is active penetration by one cell into and through a larger cel
Source: adapted from Hennes *et al.*, 2008 [22].

Figure 1. Primary parameters used for the diagnosis of Autoimmune Hepatitis (AIH).

A score of 7 or above is indicative of a definitive diagnosis of AIH, whereas a score of 6 suggests a significant likelihood of the condition. This research comprised pediatric patients who were diagnosed and verified according to the specified criteria.

In accordance with the principal objectives of this study, an investigation was conducted on pediatric individuals throughout the diagnostic process to assess their clinical manifestations. These manifestations included symptoms such as exhaustion, weakness, lethargy, numbness, nausea, stomach discomfort and itching, swollen joints, recent coagulation problem, and hepatic encephalopathy.

The selection criteria for this research were children diagnosed with AIH who provided informed permission for participation. These children were sent to the clinics of Children's Medical Center Hospital, which is connected with Tehran University of Medical Sciences (TUMS), Tehran, Iran. The study consisted of children who were assessed during the time period of 2018 to 2021 and had full information available.

The exclusion criteria encompassed several factors, including patients' unwillingness to partake in clinical studies, individuals aged 18 and above, the presence of significant non-hepatic comorbidities that could impede the completion of follow-up assessments, the need to establish that the clinical manifestations were unrelated to AIH, and the occurrence of liver and biliary system disorders unrelated to AIH, such as viral hepatitis. The individuals who met the criteria for a biopsy but were not granted permission to have the procedure were subsequently eliminated from the study. Additional exclusion criteria included anyone with a documented hypersensitivity to prednisolone or azathioprine.

The statistical measures of mean and standard deviation were used to describe the quantitative variables, while frequency and percentage were utilized to analyze the qualitative variables.

Results

This study included the evaluation of numerous factors in a cohort of 52 children diagnosed with AIH who were sent to the Children's Medical Center Hospital, affiliated to Tehran University of Medical Sciences (TUMS), located in Tehran, Iran. Therefore, a total of 52 pediatric patients were assessed, excluding those with severe and unexplained illnesses. Among the cases analyzed, the majority were female, accounting for 69.2% of the sample. The mean age of the individuals in this patient cohort was 7.76, accompanied by a standard deviation of 3.40. Nearly all the patients (71.2%) had encountered an episode of acute AIH.

Clinical manifestations

CLD was determined to be the etiology in 46.2% of the Hepatic Encephalopathy (HE) cases, as supported by empirical data. The patients had jaundice as the most prevalent first manifestation. Three other symptoms were often seen, namely weakness and lethargy (57.7%), weariness (42.3%), and stomach discomfort (57.7%). In 53.8% of the patients, no organomegaly was documented, whereas in other instances, hepatomegaly or splenohepatomegaly was observed. No individuals were found to have splenomegaly. The chart shown below illustrates the relative frequency of the aforementioned appearances. Furthermore, a majority of the patients (71.2%) did not have a prior medical history of any other disorders. However, a small percentage of cases were found to have esophageal varices (7%) and Primary Sclerosing Cholangitis (PSC) (5.8%). The following charts illustrate the relative prevalence of comorbid (or underlying) disorders. Moreover, a significant majority of the patients, namely 96.2%, possess no previous medical records indicating a viral hepatitis infection (Table 1).

Laboratory tests

The average concentration of Aspartate Transaminase (AST) was measured to be 1172.06 international units per liter (*IU/L)*, whereas the corresponding values for Alanine Transaminase (ALT) and Alkaline Phosphatase (ALP) were 948.65 *IU/L* and 804.42 *IU/L,* respectively. The average value for total bilirubin was recorded as 5.92 (*mg/dl*), whilst the specific measurement for direct bilirubin was documented as 4.32 (*mg/dl*). The prevalence of positive Antinuclear Antibodies (ANA) test results was found to be 6.3% among the cases examined. In contrast, 49% of the pediatric patients tested positive for Anti-Smooth Muscle Antibodies (ASMA). Additionally, a mere 7.8% of the cases exhibited positive blood test

Table 1. Study data

		Frequency	Percent
Gender	Female	36	69.2
	Male	16	30.8
Clinical course	Acute	37	71.2
	Chronic	15	28.8
Acute hepatic failure	Negative	28	53.8
	Positive	24	46.2
First symptom	Abdominal pain	1	1.9
	Icter	43	82.7
	LFT disturbance	6	11.5
	Malaise	1	1.9
	No symptom	1	1.9
Malaise	Negative	22	42.3
	Positive	30	57.7
Fatigue	Negative	30	57.7
	Positive	22	42.3
Abdominal pain	Negative	22	42.3
	Positive	30	57.7
Organomegaly	Without organomegaly	28	53.8
	Hepatomegaly	13	25.0
	hepatosplenomegaly	11	21.2
Comorbidity	Attention Deficit Hyperactivity Disorder (ADHD)	1	1.9
	Autoimmune hemolytic anemia	1	1.9
	Celiac	1	1.9
	DM1 and sclerosen cholangitis	1	1.9
	Esophageal varies	4	7.7
	Hypothyroidism	1	1.9
	No comorbidity	37	71.2
	Peptic ulcer	1	1.9
	Primary Sclerosing Cholangitis (PSC)	3	5.8
	Systemic Lupus Erythematosus (SLE)	2	3.8

findings for Liver-Kidney Microsomal Antibodies (LKM AB). The patients demonstrated an IgG level of 2358.6 (*mg/dl*)1, and the mean value of Gamma-Glutamyl Transferase (GGT) was 99.5 (*IU/L)* (Table 2).

Pathological examinations

All the subjects had diagnostic biopsies, and five instances not receiving biopsies were eliminated from the research. The biopsy findings in these individuals included six components, including four components pertaining to microscopic outcomes and two instances linked with grading.

The observed microscopic findings included interface hepatitis, rosette formation, emperipolesis, infiltration of lymphocytes and plasma cells, fibrose-6 scores,

Table 2. Results of the laboratory variables

	Frequency	Percent
AST (mean±SD)	1172.06 (*IU/L*)	1554.037 (*IU/L*)
ALT (mean±SD)	948.65 (*IU/L*)	1142.374 (*IU/L*)
ALP (mean±SD)	804.42 (*IU/L*)	416.307 (*IU/L*)
BILT (mean±SD)	5.922 (*mg/dl*)	6.8041 (*mg/dl*)
BILD (mean±SD)	4.329 (*mg/dl*)	5.4703 (*mg/dl*)

		Frequency	Percent
Viral hepatitis	No viral hepatitis	50	96.2
	Hepatitis A	1	1.9
	Hepatitis E	1	1.9
ANA	Negative	45 (*mg/dl*)	86.5 (*mg/dl*)
	Positive	3	5.8
Anti-SMA	Negative	26	50.0
	Positive	25	48.1
LKM Ab	Negative	47	90.4
	Positive	4	7.7
Gamma GT (mean±SD)		99.50	79.968
IgG (mean±SD)		906.771	4348
Interface hepatitis	Negative	8	15.4
	Positive	44	84.6
Rosset formation	Negative	36	69.2
	Positive	16	30.8
Emperipolesis	Negative	51	98.1
	Positive	1	1.9
Lymphocyte and plasma cell infiltration	Negative	20	38.5
	Positive	32	61.5

and HAI-18 scores.

A total of 44 patients (84.6%) exhibited interface hepatitis. Rosette formation was seen in 30.8% of the patients, specifically in 16 instances. Emperipolesis, on the other hand, was detected in a solitary case, accounting for a mere 1.9% of the whole sample. In 61.5% of the cases, there was evidence of infiltration by lymphocytes and plasma cells. The average fibrosis score observed in this cohort of patients was 2.56, derived from the analysis of six individual samples. The mean Healthcare-Associated Infection (HAI) score was determined to be 7.34 based on an analysis of 18 samples. A significant proportion of the patient cohort had received conventional therapies, namely a regimen consisting of azathioprine and prednisolone. Following the subsequent sessions, the drug regimen was terminated for an additional six individuals. Furthermore, a total of 44 patients exhibited consistent adherence to their prescribed treatment regimen. Furthermore, a total of 46 instances were reported to be in a stable state, while five people had uncontrolled therapies, and unfortunately, one individual succumbed to the illness. In a similar vein, it was found that out of the total sample size,

Table 3. Evaluation of the clinical variables and treatment outcomes

		Frequency	Percent
Fibrosis (mean±SD)		2.56	1.181
HAI score (mean±SD)		7.34	3.232
Past medical treatment	Prednisolone	2	3.8
	Azaram+Prednisolone	49	94.2
	Azaram+Prednisolone+Cyclosporine	1	1.9
Present medical treatment	No treatment	6	11.5
	Azaram	12	23.1
	Prednisolone	6	11.5
	Azaram+ Prednisolone	20	38.5
	Azaram+ Prednisolone+Cyclosporine	2	3.8
	Cellcept	1	1.9
	Prednisolone+Cyclosporin	1	1.9
	Prednisolone+Cellcept	2	3.8
	Azaram+Prednisolone+Rituximab	1	1.9
	Prednisolone+6MP	1	1.9
Prognosis	Stable	46	88.5
	Uncontrol	5	9.6
	Expired	1	1.9
Liver transplant	No transplant	50	96.2
	Candidate for transplant	1	1.9
	Transplanted	1	1.9

50 individuals did not need liver transplantation, while one case had already had the procedure, and one patient was identified as a potential candidate for liver transplantation (Table 3).

Discussion

AIH is a chronic liver disease characterized by its progressive nature and an undetermined underlying cause. This disorder has the potential to manifest at any stage of life. The condition has a variable severity that manifests in periodic fluctuations, characterized by alternating periods of heightened activity and times of relative rest. The diagnosis in this particular instance often depends on the identification of anomalies detected by histological analysis, clinical and biochemical assessments, and atypical concentrations of serum globulins, including autoantibodies (2). The first documentation of this illness dates back over half a century, and subsequent developments have led to several modifications. However, it is widely acknowledged that AIH represents the most suitable and contemporary terminology for this condition. Additionally, there exist many manifestations of co-occurrence or amalgamation of this ailment with other hepatic disorders, including primary biliary cirrhosis and primary sclerosing cholangitis (3). The characterization of these illnesses is now based on descriptive methods. Distinguishing AIH from other types of acute hepatitis is of utmost importance due to the notable proportion of patients that exhibit positive responses to anti-inflammatory treatments, immunosuppressants, or a combination of both (4). The prevalence of the condition is higher among females, with a female-to-male ratio of 1:3 in type I

and 1:8 in type II (5).

In the present investigation, it was reported that one participant had undergone transplantation, while another individual was identified as a liver transplant candidate. This finding indicates that 3.84% of the patients included in the research had received transplants, which aligns with the findings reported by van Gerven *et al* (6) (3%), as well as Malekzadeh *et al* (7) and Jiménez-Rivera *et al* (8) (5%). Cuarterolo *et al* (9) observed a prevalence of transplantation demand at 10%. As previously stated, these individuals presented with significant medical issues. The research conducted by Yeoman *et al* (10) found a liver transplant rate of 48 (n=10), with 9 cases remaining untreated. These findings underscore the need of providing treatment to these individuals.

Furthermore, a single patient succumbed to this ailment, accounting for a mortality rate of 1.9%, mirroring the findings published by Oettinger *et al* (11). Differences in values were seen across many investigations. For instance, Jiménez-Rivera *et al* (8) reported a death rate of 2.5%, which aligns with the findings of the current research. However, Yeoman *et al* (10) reported a much higher fatality rate of 20%, mostly among type II patients having acute type. Cuarterolo *et al* (9) reported an 8% death rate among individuals with CLD in their statistical population. Consequently, it was expected that there would be a rise in both complications and mortality rates. In general, the administered therapies show a statistically significant decrease of 1.9 units in the manifestation of this particular ailment. It is essential to persist in doing more studies on this ailment, since there exists the potential for a 20% rise in its worth.

The findings of the present study indicate that interface hepatitis was seen in 44 instances, accounting for 84.6% of the total sample. Furthermore, it was observed that a total of 16 individuals, accounting for 30.8% of the sample, demonstrated the occurrence of rosette formation. In a single instance, a manifestation of emperipolesis was seen, accounting for 1.9% of the cases. Furthermore, it was shown that a significant proportion of the patients, namely 61.5%, had infiltration of lymphocytes and plasma cells. It is worth noting that prior research often overlooked the inclusion of these variables in their analyses. In a study conducted by Radhakrishnan *et al* (12), it was observed that the incidence of interface hepatitis was 67%. This finding aligns with the results reported by Jiménez-Rivera *et al* (8), who documented a rate of 86%, as well as Gerven *et al* (6), who reported a rate of 87%. In relation to the occurrence of rosette formation, Jiménez-Rivera *et al* (8) observed this particular pathological feature in 18% of the patients included in their study, whereas Gerven *et al* (6) reported a prevalence rate of 16%. The precise magnitude of emperipolesis has not been determined in any of the research examined. However, Tiniakos *et al* (13) reported that it was identified as a diagnostic consequence in pathology and was detected in around 1-5% of cases. The research further revealed that the rate of rosette formation was found to be 32%, while lymphocyte and plasma cell infiltration was identified in 60-75% of the patients. In accordance with the results of the current research, Oettinger *et al* (11) reported that 52% of the cases exhibited the last variable, whereas Gerven *et al* (6) found that 75% of the patients displayed the same variable. In the research conducted by Vitfell-Pedersen *et al* (14), the diseases observed provided evidence supporting the presence of one of the aforementioned instances in 75% of the patients, thus corroborating the findings of this investigation. The aforementioned results were further corroborated by Liberal *et al* (15).

The mean fibrosis score seen in these patients was 2.56, which aligns with the findings reported in the research conducted by Smolka *et al* (16), where a score ranging from 1.9 to 3.1 was recorded. Additionally, the fibrosis score of 3 reported by Cuarterolo *et al* (9) is consistent with our current work. However, it is worth noting that the majority of studies did not provide information on the mean value of fibrosis. Instead, they just reported on the presence of fibrosis in various patients' pathology samples. For instance, van Gerven *et al* (17) reported evidence of fibrosis in 5 out of the 16 patients whose histology was studied. According to the study conducted by Malekzadeh *et al* (7), the average fibrosis score was found to be 3.9. Regarding the calculated mean age of 29.1 years in Malekzadeh *et al*'s analysis, it seems that the observed variation in the statistical population may have contributed to the divergence in the findings. The research conducted by Malekzadeh *et al* indicated that the observed variation in the findings

may be attributed to a disparity within the statistical population. Furthermore, it was anticipated that the condition would be accompanied by an increased incidence of fibrosis in the hepatic tissue. The mean value of Healthcare-Associated Infections (HAI) in the observed individuals was 7.34, whereas Oettinger *et al* (11) reported a mean value of 10. The results presented in this study are consistent with previous research findings. However, this particular variable has not been taken into account in other investigations. Nonetheless, including it into the analysis might provide more supplementary findings.

The presentations of AIH exhibit heterogeneity, perhaps characterized by fluctuations in clinical activity throughout time. Hence, the clinical manifestations of this condition often exhibit a wide range of variability, including asymptomatic cases as well as those characterized by severe symptoms and CLD. Various manifestations, such as weariness, weakness, lethargy, numbness, nausea, stomach discomfort, itching, and small-joint arthritis, are often seen. Physical exams may not provide any abnormalities; nevertheless, the presence of hepatomegaly, splenomegaly, and jaundice may indicate the presence of chronic liver disease (18). Patients who exhibit severe or fulminant symptoms, accompanied by acute jaundice and extended prothrombin time, may have ALT values above 1000 *IU/L*. Numerous juvenile patients who exhibit sudden onset manifestations of AIH often have histological indications of CLD upon biopsy. This suggests that these kids may have been exposed to a subclinical state over an extended period. The extended durations of this subclinical illness may continue to exist beyond the cessation of symptoms. Hence, it is essential to conduct more clinical investigations in order to evaluate these manifestations and maybe develop diagnostic protocols.

Conclusion

The study revealed a decrease in long-term survival rates among individuals diagnosed with AIH. There was no observed disparity in prognosis based on gender; nevertheless, it was noted that males had a shorter lifespan, maybe due to an earlier beginning of the condition. The presence of cirrhosis at first diagnosis was identified as a risk factor associated with an unfavorable prognosis, leading to an increased overall risk of mortality linked to liver dysfunction. The majority of instances of autoimmune hepatitis were seen in the female population. The average age of the patients in this study was 7.76. The majority of the patients had a sudden start of symptoms, indicating the likelihood of acute liver failure. Jaundice emerged as the prevailing first symptom. The common symptoms were weakness, lethargy, weariness, and stomach discomfort. Approximately, 50% of the patients exhibited the presence of organomegaly. A limited subset of individuals demonstrated positivity for ANA and LKM Ab. The presence of anti-SMA is seen in roughly 50% of the patients' population. Patients have significantly elevated levels of GGT and IgG. In majority of the instances, there exists evidence of disease. The mean fibrosis score seen in the patient cohort was 2.56, while the average HAI score was calculated based on 29 examinations. One patient succumbed to the condition, another patient underwent transplantation, and a third patient was identified as a candidate for liver transplantation. The majority of patients had conventional standard therapies, namely, the administration of a combination of azathioprine and prednisolone.

The presentations of AIH exhibit heterogeneity, perhaps characterized by fluctuations in clinical activity throughout time. As a result, these clinical presentations often exhibit a wide range of variability, including both asymptomatic cases and those with severe symptoms, including CLD. Various manifestations, including weariness, weakness, lethargy, numbness, nausea, stomach discomfort, itching, and small-joint arthritis, are often seen. Physical exams may also reveal the absence of any abnormalities, whereas the presence of hepatomegaly, splenomegaly, and jaundice may indicate CLD. Patients presenting with severe or fulminant symptoms, accompanied by acute jaundice and extended prothrombin time, may have ALT values above 1000.

A considerable number of juvenile patients who have sudden onset manifestations of AIH exhibit histological indications of CLD upon biopsy. This suggests that they could have been exposed to a subclinical illness over an extended period. The extended durations of this subclinical ailment may

continue to endure beyond the cessation of symptoms. In order to achieve this objective, it is essential to conduct more clinical investigations to assess these manifestations and maybe develop diagnostic protocols.

Ethical Statement

Ethical code: IR.TUMS.CHMC.REC1399.089.

Conflict of Interest

The authors declare that there is no conflict of interest.

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