RESEARCH ARTICLE

Clinical spectrum and outcomes of autoimmune hepatitis in children: a quaternary centre experience

Nazia Iqbal, Iqtadar Seerat, Sobia Noureen, Hassan Bashir

Abstract

Objective: To analyse paediatric autoimmune hepatitis with respect to disease severity, treatment response, and clinical outcomes, including progression to liver failure and transplant survival.

Method: The retro-prospective study was conducted at the Pakistan Kidney and Liver Institute and Research Centre, Lahore, Pakistan, and comprised data from July 2019 to December 2024 of paediatric patients aged <15 years diagnosed with autoimmune hepatitis. Demographic characteristics, clinical manifestations as well as laboratory and imaging findings were noted. Data was analysed using SPSS 27.

Results: Of the 56 patients, 30(53.6%) were girls with mean age 9.94±2.63 years, and 26(46.4%) were boys with mean age 9.24±2.90 years. Autoimmune hepatitis type 1 was the predominant type 46(82.1%), while type 2 was found in 1(1.8%) patient and 9(16.1%) were seronegative. Jaundice was the most common symptom found in 54(96.4%) followed by ascites 28(50%) and abdominal pain 18(32.1%). Histopathology of liver biopsies revealed features consistent with autoimmune hepatitis including statistically significant hepatocyte rosette formation (p-value= 0.100). Overall, 8 (14.3%) patients required liver transplantation.

Conclusion: The clinical spectrum of autoimmune hepatitis and its outcomes in children indicated there were significant diagnostic and therapeutic challenges that needed to be overcome.

Key Words: Autoimmune diseases, Autoantibodies, Immunosuppressive agents, Liver biopsy, Liver transplantation.
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Introduction

Autoimmune hepatitis (AIH) is a long-lasting, inflammatory condition of the liver that is characterised by the destruction of liver cells, and worsens over time.[1-3] While its precise cause remains unknown, the disease is thought to develop when the immune system mistakenly attacks the liver, likely influenced by external factors, such as viral infections, medications, dietary deficiencies, toxins, drugs, alcohol, smoking, ionising radiation, and air pollution, in genetically predisposed individuals, possibly inducing critical epigenetic modifications.[1,4,5]

If left untreated, it can progress to severe complications, including cirrhosis, impaired liver function and liver cancer, and may even have fatal outcomes. This condition can develop in individuals of any age, racial background or ethnic group. While it affects both males and females, it disproportionately impacts women, with girls aged <18 accounting for 60-76% of paediatric cases. Genetic predisposition plays a role, as 40% of patients report a family history of AIH. Additionally, 20% of those diagnosed have coexisting autoimmune disorders.[3-6] Worldwide, AIH affects 100,000-200,000 people annually, with incidence rates of 0.2-2/100,000 and a prevalence of 11-25/100,000.[1,2,4,7]

AIH is classified into distinct subtypes. Type 1 is marked by the presence of antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA). Type 2 is characterised by anti-liver kidney microsomal (LKM) or anti-liver cytosol antibodies (LCA). Diagnosis of AIH in paediatrics is based on a combination of clinical features, elevated aminotransferases, hypergammaglobulinaemia, positive autoantibodies, and compatible histology, supported by treatment response. In seronegative AIH, autoantibodies are absent, but clinical, biochemical and histological features as well as treatment response align. The primary objectives of initial therapy are to relieve symptoms, halt disease advancement, attain biochemical remission, and minimise the risk or severity of associated complications. [2-11] Treatment focusses on suppressing the immune system, typically starting with prednisone alone or paired with azathioprine. For severe cases, like acute liver failure, unresponsive to steroids or advanced cirrhosis, a liver transplant becomes the last-resort option.[11,12] Despite cessation of treatment and restoration of standard diagnostic parameters, ongoing follow-up remains essential throughout the patient's life.[10-13]

Department of Paediatric Gastroenterology and Hepatology, Pakistan Kidney and Liver Institute and Research Centre, Lahore, Pakistan.
Correspondence: Nazia Iqbal. **Email:** dr.naz.pk1@gmail.com
ORCID ID: 0009-0009-7418-6235

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AIH remains an under-recognised but significant cause of paediatric liver disease in Pakistan, where scarce epidemiological data and low clinical suspicion often lead to delayed diagnosis.[2]) Despite being less common than viral or metabolic liver conditions, AIH warrants careful clinical consideration once common causes of liver disease are excluded.

The current study was planned to analyse paediatric AIH with respect to disease severity, treatment response, and clinical outcomes, including progression to liver failure and transplant survival.

Materials and Methods

The retro-prospective study was conducted at the Pakistan Kidney and Liver Institute and Research Centre, Lahore, Pakistan, and comprised data from July 2019 to December 2024 of paediatric patients aged <15 years diagnosed with autoimmune hepatitis. Data of patients with chronic liver disease from alternative causes, including viral or drug-induced hepatitis and metabolic disorders, was excluded.

Demographic and clinical data, including age, gender, clinical symptoms, laboratory evaluations, biopsy results and imaging modalities, was documented using a comprehensive proforma. Data was retrieved after approval from the institutional ethics review committee from 4th April 2024 to 31st December 2024.

Data was analysed using SPSS 27. Categorical variables, like gender, presenting symptoms etc., were presented as frequencies and percentages, and they were analysed using chi-square or fisher's exact test as per statistical assumptions. Numerical data normality was assessed using the Shapiro-Wilk test. Data not normally distributed was presented as median with interquartile range IQR), while data normally distributed was presented as mean ± standard deviation (SD). To determine the difference according to survival status in numerical variables, like total bilirubin, Aspartate aminotransferase, Alanine aminotransferase etc., nonparametric, Mann Whiteny U test was used. For comparison between baseline and post-treatment values, Wilcoxon signed-rank test was applied. P<0.05 was considered statistically significant.

Results

Of the 56 patients, 30(53.6%) were girls with mean age 9.94±2.63 years, and 26(46.4%) were boys with mean age 9.24±2.90 years. The boys had a mean weight of

Table-1: Clinical presentation of autoimmune hepatitis (AIH) (n=56).

Presentation		Autoimmune Hepatitis	Sero-positive (n=47)		Sero-negative (n=9)		p-value
		n(%)	Boy n(%)	Girl n(%)	Boy n(%)	Girl n(%)	
Jaundice	Yes	54(96.4)	22(95.7)	24(100)	2(66.7)	6(100)	0.211
	No	2(3.6)	1(4.3)		1(33.3)		
Ascites	Yes	28(50.0)	11(47.8)	12(50.0)	2(66.7)	3(50.0)	0.608
	No	28(50.0)	12(52.2)	12(50.0)	1(33.3)	3(50.0)	
UGIB	Yes	15(26.8)	7(30.4)	7(29.2)	1(33.3)	0	0.531
	No	41(73.2)	16(69.6)	17(70.8)	2(66.7)	6(100)	
Oedema	Yes	6(10.7)	4(17.4)	2(8.3)			0.293
	No	50(89.3)	19(82.6)	22(91.7)	3(100)	6(100)	
Anorexia	Yes	9(16.1)	2(8.7)	6(25.0)	1(33.3)		0.481
	No	47(83.9)	21(91.3)	18(75.0)	2(66.7)	6(100)	
Fever	Yes	20(35.7)	7(30.4)	9(37.5)	1(33.3)	3(50.0)	0.580
	No	36(64.3)	16(69.6)	15(62.5)	2(66.7)	3(50.0)	
Joint pains	Yes	7(12.5)	2(8.7)	4(16.7)	1(33.3)	0	>0.999
	No	49 (87.5)	21(91.3)	20(83.3)	2(66.7)	6(100)	
Abdominal pain	Yes	18(32.1)	6(26.1)	7(29.2)	2(66.7)	3(50.0)	>0.999
	No	38(67.9)	17(73.9)	17(70.8)	1(33.3)	3(50.0)	
Fatigue	Yes	5(8.9)	1(4.3)	2(8.3)	1(33.3)	1(16.7)	>0.999
	No	51(91.1)	22(95.7)	22(91.7)	2(66.7)	5(83.3)	
Encephalopathy	Yes	8(14.3)	4(17.4)	4(16.7)			0.827
	No	48(85.7)	19(82.6)	20(83.3)	3(100)	6(100)	
Hepatomegaly	Yes	30(53.6)	13(56.5)	11(45.8)	1(33.3)	5(83.3)	>0.999
	No	26(46.4)	10(43.5)	13(54.2)	2(66.7)	1(16.7)	
Splenomegaly	Yes	34(60.7)	14(60.9)	14(58.3)	2(66.7)	4 (66.7)	>0.999
	No	22(39.3)	9(39.1)	10(41.7)	1(33.3)	2(33.3)	

Chi-square test, * p-value significant at 0.05
UGIB: Upper gastrointestinal bleeding.

Table-2: Comparison of lab parameters pre and post-treatment.

Presentation	Autoimmune Hepatitis					
	Sero-positive			Sero-negative		
	Pre-treatment Median (IQR)	Post treatment Median (IQR)	p-value	Pre-treatment Median (IQR)	Post treatment Median (IQR)	p-value
Total bilirubin	4.4(1.3-13.8)	0.7(0.5-1.0)	<0.001*	1.9(1.1-7.7)	0.5(0.3-0.9)	0.008*
Direct bilirubin	3.6(0.8-10.1)	0.5(0.3-0.8)	<0.001*	1.0(0.7-4.4)	0.2(0.2-0.7)	0.008*
ALT	127.0(65.0-366.0)	41.0(26.0-49.0)	<0.001*	84.0(53.5-245.5)	40.0(26.0-48.5)	0.051
AST	188.0(78.0-589.0)	40.0(32.0-59.0)	<0.001*	145.0(81.5-528.5)	49.0(36.5-51.5)	0.038*
ALP	311.0(250.0-470.0)	214.0(167.0-316.0)	<0.001*	508.0(378.5-765.0)	290.0(237.0-480.0)	0.028*
GGT	87.0(49.0-172.0)	43.0(32.0-77.0)	<0.001*	70.0(40.5-157.0)	36.0(25.5-127.5)	0.263
Albumin	3.2(2.6-3.9)	3.7(3.2-4.2)	<0.001*	2.9(2.4-4.0)	4.1(3.5-4.4)	0.008*
INR	1.4(1.1-2.1)	1.1(1.0-1.2)	<0.001*	1.3(1.0-1.9)	1.0(0.9-1.3)	0.058
Haemoglobin	10.0(9.2-12.0)	11.8(11.0-12.0)	0.001*	10.8(7.6-11.3)	11.6(10.7-12.0)	0.012*
Platelets	171.0(90.0-311.0)	201.0(134.0-295.0)	0.172	138.0(67.5-344.5)	200.0(140.0-302.5)	0.401

Wilcoxon Signed-Rank Test, *p-value significant at 0.05
AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: Alkaline phosphatase. GGT: gamma glutamyltransferase, INR: international normalised ratio, IQR: Interquartile range.

Table-3: Liver biopsy findings and staging of fibrosis.

Histopathology findings	Outcome	Sero-Positive AIH (n=41) n (%)	Sero-negative AIH (n=9) n (%)	Total (n=50)	p-value
Interphase hepatitis	Yes	37(90.2)	9(100.0)	46(92.0)	0.189
	No	4(0.09)	0(0.0)	4(8.0)	
Bridging fibrosis	Yes	17(41.4)	3(33.3)	20(40)	>0.999
	No	24(58.5)	6(66.7)	30(60)	
Rossette formation	Yes	11(26.8)	5(55.6)	16(32)	0.100
	No	30(73.1)	4(44.4))	34(68)	
Piecemeal necrosis	Yes	12(29.2)	3(33.3)	15(30)	0.688
	No	29(70.7)	6(66.7)	35(70)	
Lymphoplasmacytic infiltrate	Yes	35(85.3)	8(88.9)	43(86)	0.668
	No	6(14.6)	1(11.1)	7(14)	
Stage of fibrosis	F0	8(19.5)	0(0.00)	8(16)	0.268
	F1	3(7.3)	2(22.2)	5(10)	
	F2	8(19.5)	3(33.3)	11(22)	
	F3	11(26.8)	2(22.2)	13(26)	
	F4	11(26.8)	2(22.2)	13(26)	

Chi-square test, * p-value significant at 0.05

28.7±11.4kg and a mean height of 131.0±19.9cm compared to girls' 29.3±10.6kg and 128.9±16.3cm, respectively. Jaundice was the most common symptom found in 54(96.4%) followed by ascites 28(50%) and abdominal pain 18(32.1%). Overall, 47(84%) patients were seropositive, while 9(16%) were seronegative, and there was no significant difference between them in terms of clinical manifestations (Table 1).

AIH type 1 was the predominant type 46(82.1%), while type 2 was found in 1(1.8%) patient and 9(16.1%) were seronegative. Baseline laboratory parameters exhibited no significant variations across the study groups, but significant improvement (p<0.05) was seen in nearly all parameters post-treatment (Table 2).

Median alkaline phosphatase was higher in seronegative AIH i.e. 508.0(378.5-765.0)U/L compared to seropositive i.e. 311.0(250.0-470.0) U/L, suggesting potential cholestasis or overlap syndrome. Primary sclerosing cholangitis was found in 5(8.9%) patients, and, of them, 3(60%) had type 1 AIH and 2(40%) had seronegative AIH. Median albumin was lower in seronegative AIH 3.2(2.6-3.9) mg/dL i.e. compared to seropositive AIH patients i.e. 2.9(2.4-4.0) mg/dL), indicating possible synthetic dysfunction. (Table 2)

ANA was positive in 43(76.7 %), ASMA in 9(16%) and anti-LC in 1(1.7%) patient. Further, 45(80.3%) patients had

immunoglobulin G (IgG) levels >17g/dl, and 11(19.6%) had normal IgG levels. Fulminant disease course was seen in 5(8.9%) children, and anaemia in 14(25%) which was caused mainly by hypersplenism in 6(10.7%) and iron deficiency anaemia in 5(8.9%) patients. Thrombocytopenia was observed in 12(21.4%) patients, including 3 (25%) without significant portal hypertension.

Liver biopsy was performed in 50(89.3%) patients which showed findings compatible with AIH (Table 3) In 6(10.7%) patients it was not performed due to high initial international normalised ratio (INR), but were treated for presumed AIH and demonstrated a good response to corticosteroid therapy. There was no statistically significant differences in most histopathology findings between seropositive and seronegative AIH, except Rosette formation (p-value 0.100). Advanced liver fibrosis was found in 26 (46.4%) patients. No hepatic fibrosis was seen in 8(14.2%) patients. Liver ultrasound revealed a heterogeneous echotexture in 42 of the 56 patients (75%). Magnetic resonance cholangiopancreatography (MRCP) was available for 12(21.4%) patients.

Regarding treatment, all 56(100%) patients received prednisolone initially, followed by combined prednisolone and azathioprine drugs. Treatment was effective for the majority of patients, with 43 (76.7%) achieving complete remission and 8 (14.2%) achieving partial remission. However, 3 patients (5.3%) died while on treatment. Long-term follow-up was hindered by significant logistical and financial barriers, particularly for patients from remote areas, contributing to loss to follow-up. No remission was seen in 5(8.9%) patients ultimately necessitating liver transplantation. Patients without cirrhosis 8 (14.2%) responded well to treatment and all of them achieved remission. Twenty seven patients (48.2%) with compensated cirrhosis achieved remission. Eight Patients (14.3%) with decompensated cirrhotic disease achieved remission after liver transplantation. Surprisingly, remission was achieved in 2(3.5%) patients diagnosed with decompensated cirrhosis and biopsy-confirmed F4 fibrosis despite the severity of their condition. Also, 5 (8.9%) patients with acute liver failure achieved remission on medical treatment. Live donor Liver transplantation was performed in 8(14.3%) patients and all of them were doing well.

Discussion

AIH is a chronic inflammatory condition where the immune system malfunctions and attacks healthy liver cells, leading to liver damage. To our knowledge, the current study comprises the largest cohort of Pakistani children with AIH to date, aiming at bridging critical gaps in regional epidemiological and clinical understanding.

Like in most parts of the world, autoimmune hepatitis in the study affected more girls (53.6%) than boys. This matches what has been observed in other countries, where AIH tends to be more common in girls regardless of ethnicity and age.[1-21] Sex hormones appear to play a key role, potentially influencing immune responses and activating certain genes on the X chromosome. Other factors, like gut bacteria and epigenetic changes, may also contribute.[1] A significant finding of this study was the 73.2% positive consanguinity rate, exceeding those reported earlier (58.3%), likely attributable to the high prevalence of consanguineous marriage in Pakistan. Additionally, 10.7% of the current patients had a family history of liver disease, a finding consistent with literature (16.6%).[16]

Patients with AIH have variable presentations ranging from insidious to acute and fulminant.[4-10] Notably, none of the current patients were asymptomatic. Surprisingly, every child in the study was diagnosed only after symptoms appeared, often with advanced liver damage, including cirrhosis, aligning with Ferronato M et al.[17] (35-45%) and Maharaj Y et al.[13] (50%). Surprisingly, despite these late diagnoses, most of the current patients responded well to standard treatments, a pattern mirroring findings from sub-Sahara African cohorts, but contrasting with reports from high-income countries, where subclinical presentations are more common.[4] This disparity likely reflects socioeconomic barriers to healthcare access in developing regions, where diagnoses often occur only after symptoms emerge.[5-13]

In the current study, five children presented for the first time in acute liver failure (ALF) and were subsequently diagnosed with AIH. The remaining patients presented with a chronic, slowly progressive disease. Clinical features did not differ significantly between the subtypes. Coeliac disease occurred in three patients, one had autoimmune thyroiditis and one presented with diabetes mellitus. Two patients with ulcerative colitis demonstrated characteristics consistent with AIH-overlap syndrome. Recognised conditions associated with AIH include systemic lupus erythematosus (SLE), autoimmune dermatological disorders, autoimmune polyendocrinopathy syndrome and lymphoproliferative diseases.[14-20]

For patients with AIH refractory to medical therapy, liver transplantation serves as a viable and effective therapeutic intervention. Eight (14.2%) patients in the current cohort underwent live donor liver transplantation. The pillar of AIH therapy is immunosuppression, with steroid therapy recognised as the gold standard. Azathioprine is usually added to therapy as the so-called steroid-sparing agent.[15-20] Almost all the current patients had a good response to the standard treatment with prednisolone, with or without azathioprine, regardless of the severity of the liver disease.

Patients with acute severe AIH and ALF require immediate treatment with corticosteroids and close assessment of treatment response to determine the need for urgent liver transplant.[20,21]

The current study has limitations as it had a small sample size with a short follow-up at a single centre. Besides, given the retrospective design of the study, some evaluations were weakened by missing data. To strengthen the evidence base and identify predictors of adverse events, future research should focus on conducting larger, multicentre studies with prolonged follow-up.

Conclusion

A Jaundice was the most common presenting symptom among the patients. Those with ALF and compensated cirrhosis responded positively to medical treatment. In Pakistan, where paediatric AIH data remains scarce, the disease's progressive nature and risk of complications demand urgent attention.

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AUTHORS' CONTRIBUTIONS:

NI, IS, SN & HB: Concept, design, data acquisition, analysis, interpretation, drafting, revision, final approval and agreement to be accountable for all aspects of the work.