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BRIEF REPORT

AUTOIMMUNE LIVER DISEASE IN CHILDREN

Aarti Rahangdale.

Consultant Pediatrician, Aadhya Multispecialty Hospital, Gondia, Maharashtra, India.

ABSTRACT

Autoimmune hepatitis (AIH) is characterized by inflammatory liver histology, circulating-non-organ specific autoantibodies and increased level of transaminases and serum immunoglobulins in absence of a known etiology. Two types of AIH have been described – Type-1 AIH which has positive smooth muscle antibody (SMA) and/or antinuclear antibody (ANA) & Type-2 AIH which has antibodies to liver-kidney microsomal (anti-LKM). Both types have female preponderance. We report a series of 6 patients (5 girls, 1 boy) with AIH (5 Type-1 AIH & 1 Type-2 AIH) who had varied presentations (5 patients presented with jaundice of which 4 patients had acute symptoms and one had jaundice for 2 months. Two patients had recurrent episodes of jaundice and one patient with Type-2 AIH had failure to thrive with hepatosplenomegaly and alopecia partialis). Three patients with AIH Type-1 were treated with oral prednisolone and had normalization of liver enzymes within 6 months of therapy and are in remission. Remaining 3 patients refused treatment. All other causes of liver disease including viral hepatitis, Wilson's disease were ruled out in these patients.

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Introduction

Autoimmune liver disorders of childhood are inflammatory liver diseases characterized histologically by a dense mononuclear cell infiltrate in the portal tract and serologically by the presence of non-organ and liver specific autoantibodies and increased levels of transaminases and IgG in the absence of a known etiology.[1] Autoimmune liver diseases in childhood includes autoimmune hepatitis (AIH) and primary (Autoimmune) Sclerosing Cholangitis [P(A) SC]. Both diseases are characterized by a chronic, immune-mediated liver inflammation involving mainly hepatocytes in AIH and bile ducts in PSC. Both diseases, if untreated, lead to liver cirrhosis.[2] AIH could be classified, according to the autoantibodies pattern, into two subtypes: AIH-1 characterized by presence of smooth muscle (SMA) and/or antinuclear (ANA) antibodies whereas AIH type-2 is positive for anti-liver-kidney microsomal type 1 (anti LKM-1) antibody.[3] We present a series of 6 cases who presented to our pediatric liver clinic with jaundice and/or chronic liver disease and were detected to have AIH.

Case 1: A 5-year-old girl presented with abdominal swelling and jaundice for 5 months. There were no bleeding manifestations or altered sensorium. She had pleural effusion 3 months ago and was treated with antibiotics. On examination, she had hepatosplenomegaly, jaundice, Bitot's spots, angular cheilitis and decreased air entry in right inframammary region with crepitations in same area. Investigations are depicted in Table 1. Her Chest X-Ray showed right mid zone consolidation. Mantoux test was negative. Liver biopsy showed loss of architecture with vacuolar change, spotty neurosis and periportal inflammation [HAI: 6]. Patient was started on antituberculosis therapy (ATT) in view of non-resolving pneumonia with pleural effusion and after 2 weeks of ATT, oral prednisolone (2 mg/kg/day) were added. Prednisolone was gradually tapered to 0.5 mg/kg/day in next 6 months and she was continued on the same. Her liver function tests had normalized by 6 months of therapy and Chest X-Ray also improved.

Case 2: A 3½ years old girl presented with jaundice and fever for 8 days. She had suffered an episode of jaundice with ascites and hematochezia at 2½ years of age. At that time, her serum bilirubin was 12.9 mg/dl (direct bilirubin = 6.4 mg/dl), SGOT = 745 IU/L, SGPT = 386 IU/L, Total proteins = 5.6 gm/dl with albumin of 2.6 gm/dl. HBsAg, Hepatitis E IgM, Hepatitis A IgM, Hepatitis C Antibody were negative. Her ANA was 1:40 and ds DNA was negative. She responded to symptomatic treatment. Currently, she had hepatomegaly and jaundice on examination. Other systems were normal. Her current investigations are depicted in Table 1. Liver biopsy showed marked inflammation with cirrhosis. She was advised about steroid therapy but was subsequently lost to follow up as patient was from another town.

Case 3: A 5-year-old girl presented with abdominal distension and failure to thrive for 1 year. She had been treated with antituberculosis therapy at 3½ years of age for 6 months. She was immunized up to age and milestones were normal. On examination, height was 94 cms, weight was 11 kg (<5th centile). She had alopecia partialis, pallor and splenohepatomegaly.

Address for Correspondance: Aarti Rahangdale
Aadhya Multispecialty Hospital, Ring Road, Rajabhoj Colony, Gondia 661614, Maharashtra, India.
Email: dr.aarti.r@gmail.com

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Other systems were normal. Investigations are depicted in Table 1. A liver biopsy showed chronic active hepatitis. She was advised steroids but was lost to follow up. She subsequently again presented after 6 months. At that time too, her liver functions were normal except for hypoalbuminemia (Albumin = 3 gm/dl). She was again advised regarding steroids but again was lost to follow up.

Case 4: A 7-year-old girl hailing from Bihar (area endemic for visceral leishmaniasis) presented with fever for 6 months, abdominal distension for 3 months and jaundice for 1 week. There was no darkening of skin, bleeding manifestations. On examination, height was 115 cm; weight was 15 kg (<5th centile). She had jaundice with hepatosplenomegaly. Other systems were normal. In view of clinical suspicion of kalaazar a bone marrow examination was done which showed no LD bodies. A liver biopsy was also done that showed severe degenerative changes in ballooned hepatocytes with giant cell hepatitis. There were no LD bodies. Other investigations are depicted in Table 1. Her HIV, Dengue, Leptospira ELISA were also negative. She was treated with miltefosine in view of clinical suspicion of kalaazar following which her liver and spleen regressed and hemogram also normalized. However she continued to have jaundice (bilirubin = 2.5 mg/dl) and repeat ANA was ++++ (1:40 dilution). She was then advised steroids which parents refused.

Case 5: A 2½ years old boy born on non-consanguineous marriage presented with jaundice for 2 months, abdominal distension and excessive sleepiness for 2 days. On examination, she had pallor, jaundice, ascites, and hepatomegaly. Other systems were normal. Investigations are depicted in Table 1. Hepatitis A IgM was positive and serum ammonia was normal. Patient was treated with L-Ornithine, L-Aspartate and Lactulose along with multivitamins. Her bilirubin decreased to 5.5 mg/dl and SGOT decreased to 48 IU/L, SGPT to 44 IU/L in next 20 days. A liver biopsy was subsequently done that showed mild architectural alteration with vacuolar change and mild neutrophilic exudates and portal bridging (HAI: 4) suggestive of autoimmune hepatitis. Even after 6 months of acute hepatitis, ANA remained positive and SGOT was 52 IU/L, SGPT was 41 IU/L and bilirubin was 1.7 mg/dl. He continued to have hepatomegaly and developed splenomegaly. He was thus started on oral prednisolone (1 mg/kg/day) which was tapered and omitted after 1½ years. His liver function tests had completely normalized.

Table 1. Investigations of all patients.

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**
Hemoglobin (gm %)	5.5	10.2	7.1	7.9	8	12.8
WBC (cells/cumm)	16,100	18,500	22,700	3000	15,700	12,200
Platelets (cells/cumm)	2,94,000	6,74,000	1,57,000	55,000	3,28,000	4,47,000
ESR (mm at end of 1 hr)	50	-	-	-	-	-
Bilirubin (mg/dl)	1.0	12.8	0.6	10.1	22.8	7.4
SGOT (IU/L)	139	2636	27	2405	660	865
SGPT (IU/L)	107	1135	12	1185	490	785
Total proteins (gm/dl)	6.8	7.0	6.7	6.8	5.8	7.0
Albumin (gm/dl)	3.1	3.7	3.0	2.2	2.9	4.5
Alkaline Phosphatase (IU/L)	171	739	-	519	226	482
HBsAg	Negative	Negative	Negative	Negative	Negative	Negative
Anti-Hepatitis C	Negative	Negative	Negative	Negative	Negative	Negative
ANA	Positive (1:40)	Negative	Negative	Positive (1:80)	Low positive	Positive
ds DNA	Positive (69.5 µ/ml)	Negative	Negative	-	-	-
Anti-smooth muscle antibody	Negative	Positive	Negative	Negative	Negative	Positive
Anti LKM	Negative	Negative	Positive	Negative	Negative	Positive
24 hr urine copper	-	-	Normal	Normal	Normal	Normal
C_3	46	-	-	-	-	-
USG Abdomen	Hepatosplenomegaly. No portal hypertension	Hepatomegaly	Splenohepatomegaly with portal hypertension	Splenohepatomegaly	Hepatosplenomegaly with ascites	Hepatosplenomegaly

Case 6: A 4-year-old girl presented with jaundice for 15 days and clay-colored stools for 8 days. She had recurrent jaundice with first episode at 1½ years of age, 2nd episode at 2¼ years of age and 3rd episode at 3 years 10 months of age. She had been investigated for same and detected to have ANA and anti smooth muscle antibody positive at 2½ years of age. However she was not on any treatment. On examination, height was 96 cm; weight = 15 kg. She had jaundice, hepatomegaly, and ascites. Other systems were normal. Investigations are depicted in Table 1. Liver biopsy showed cirrhosis with marked inflammation with PAS positive granules. Her alpha-1 antitrypsin levels were normal. She was started on oral prednisolone 1 mg/kg/day which has now been tapered to 0.5 mg/kg/day. She is on treatment for past 1 year and her liver function tests are normal. She is on regular follow up.

Discussion

Autoimmune liver disease in children has been reported previously from India in 2001 in 6 children and constituted 3.9% of chronic liver diseases cases at that centre with 4 patients presenting as acute hepatitis like presentation.[4] However there are 3 clinical patterns of disease onset - (a) in at least 40% of patients, the presentation is similar to that of an acute viral hepatitis; (b) in 25-40% of patients, the onset is insidious with an illness characterized by progressive fatigue and relapsing jaundice and; (c) in about 10% of patients there is no history of jaundice and diagnosis is established following identification of portal hypertension.[3] Similarly in our 6 patients, 5 patients presented with jaundice of which 4 patients presented with acute symptoms of which 2 patients had previous episodes of jaundice in past. One patient had jaundice for 2 months. The only child who did not present with jaundice had symptoms of failure, to thrive with hepatosplenomegaly with alopecia and positive anti LKM antibodies suggestive of type-2 AIH. Thus mode of presentation of AIH in childhood is variable and disease should be suspected and excluded in all children presenting with symptoms and signs of prolonged or severe liver disease.[1]

Type-1 AIH represents two thirds of the cases and is a disease of children and adults while type-2 is mainly described in children. Severity of disease is similar in the two types of AIH.[3] Similarly in 5 patients in our series, type-1 AIH was detected whereas in one patient, type-2 AIH was detected. Type-2 AIH can be associated to autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), an autosomal recessive disorder characterized by a variety of organ specific autoimmune disorders.[5] Though our patient with Type-2 AIH did not have hypoparathyroidism or candidiasis, she did have alopecia partialis suggestive of hair related autoimmune disorder. Other autoimmune disorders associated with both types of AIH are thyroiditis, inflammatory bowel disease, vitiligo, insulin dependent diabetes and nephritic syndrome.[3]

The course of the disease can be fluctuating with flares and spontaneous remissions[1] which is similar in 2 of our patients where they had recurrent jaundice. In a study from Australia, it was found that 86% of patients have hepatomegaly on presentation, 66% have jaundice and 50% have splenomegaly.[6] Similarly in our series, 83% had jaundice, 100% had hepatomegaly and 50% had splenomegaly. There is a female preponderance in both types of AIH.[7] In our series, all except one patient were girls.

Diagnosis of AIH is established by histological finding of interface hepatitis with massive portal infiltration of mononuclear cells and plasmocytes, circulating non-organ specific autoantibodies and increased level of immunoglobulins in absence of a known etiology.[2,7] Similarly in our patients, ANA was positive in 4 patients, SMA was positive in 2 patients and LKM was positive in one patient. All other causes of liver disease were ruled out and liver biopsy showed marked inflammation in all except the one in which Kala azar was suspected. Though we did not do immunoglobulins in our patients due to unaffordability, serum globulins were elevated in all patients giving an indirect pointer towards hypergammaglobulinemia.

Standard treatment of AIH consists of prednisolone (2 mg/kg/day) which is gradually decreased over a period of 4 to 8 wk with progressive normalization of the transaminases, and then the patient is maintained on the minimal dose usually 2.5 mg/d or 5 mg/d depending on the age that is able to sustain normal transaminase levels.[3,8] If progressive normalization of liver function tests is not obtained over this period of time or if too high a dose of prednisolone is required to maintain normal transaminases, azathioprine is added at a starting dose of 0.5 mg/kg/day which is gradually increased to 2-2.5 mg/kg/day till biochemical control is achieved.[1] In our patients, steroids were started in 3 patients and all of them had normalization of liver enzymes in 6 months and none required azathioprine which is similar to that of the King's series.[3] Cessation of treatment is considered if liver biopsy shows minimal or no inflammatory change after at least one year of normal liver function tests.[1] In patient's refractory to azathioprine and steroids, other drugs such as mycophenolate mofetil, cyclosporine A or tacrolimus can be considered.[1]

Conclusion

Although AIH is uncommon in children, it should be considered in the differential diagnosis of patients with acute or chronic liver disease. Diagnosis with non-organ specific antibodies and inflammatory changes on liver biopsy are highly suggestive. Treatment with long term immunosuppressive therapy can be challenging.

Compliance with Ethical Standards

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