Acute viral hepatitis-A, triggering the occurrence of autoimmune hepatitis

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Introduction

Acute viral hepatitis A is generally self-limiting and does not show chronicity in most cases[1]. Cases have been reported where hepatitis A was considered a trigger for the occurrence of autoimmune hepatitis (AIH) owing to the theory of viral protein being similar to an amino-acid chain of various autoantibodies leading to cross-immune reactions damaging the liver parenchyma[2]. Presence of autoantibodies and the hallmark changes in liver parenchyma on histopathology and hyper-gammaglobulinaemia are the characteristics of AIH[3]. AIH in children is uncommon, with an incidence of 0.1 - 0.23 per 100,000 children[4]. Based on circulating autoantibodies, AIH is classified into two types. Type I has antinuclear antibody (ANA) and/or anti smooth muscle antibody (SMA), whereas type II has anti liver kidney microsomal (LKM) antibody-I and/or anti LKM antibody-III and/or anti liver cytosol-I[5]. Type I AIH is commoner than type II, constituting about 80% of all cases[5]. We report a four-year-old boy presenting with fatiguability, icterus and elevated liver enzymes who was initially diagnosed as acute hepatitis A, but presented with similar complaints three months later and was diagnosed to have AIH.

Case report

A 4-year-old boy presented with fever, fatiguability and anorexia for 5 days, dark coloured urine and pale stools for 3 days and icterus for 2 days with no similar history in the past. He was immunized for hepatitis B and had no history of blood transfusions. On admission, child weighed 14 kg and had a height of 112 cm which was appropriate for his age. He was afebrile with a pulse rate of 84/min, respiratory rate of 22/min and an oxygen saturation of 94% in room air. Liver was palpable 3 cm below costal margin with soft consistency and spleen was palpable 1 cm below the costal margin with no other systemic abnormalities. His haemoglobin level was 10.4g/dL, total leucocyte count was 8200/cu mm and platelet count was 280,000/cu mm. His liver function tests (LFTs) showed a total serum bilirubin (TSB) 8mg/dL (conjugated 6.7mg/dL), aspartate transaminase (AST) 139 U/L (normal range 15-40 U/L) and alanine transaminase (ALT) 73 U/L (normal range 5-45 U/L). C-reactive protein (CRP) was 2mg/dL. His abdominal sonography showed mild hepatomegaly with normal echotexture, normal gallbladder and no other abnormalities. Immunoglobulin M antibodies to hepatitis A virus were positive and he was treated palliatively. His LFTs started to improve after 3 days (TSB 4 mg/dL, conjugated SB 3mg/dL, ALT 40 U/L and AST 68 U/L). He was discharged after 7 days of admission and advised to come for regular follow up.

Three months later, child presented with icterus and dark urine for 3-4 days. He was afebrile, with a pulse rate of 88/min, respiratory rate of 20/min and oxygen saturation of 96% in room air. Liver was palpable 5cm below the costal margin with firm consistency and spleen was palpable 1cm below the costal margin. Rest of the examination was normal. TSB was 8.1mg/dL (conjugated 6.7 mg/dL), AST 139 U/L and ALT 75 U/L. Ultrasonography of abdomen showed an enlarged liver with altered echotexture and dilated portal vein, but no intrahepatic cholestasis or abnormality in the gallbladder. He was started on ursodeoxycholic acid (20 mg/kg/day twice a day), vitamin A (10,000-15,000 IU/day once daily), vitamin D (50-400 IU/day once daily), vitamin E (5000-8000 IU/day) and vitamin K (2.5-5 mg). Metabolic diseases affecting the liver, like haemochromatosis and Wilson disease were ruled out as serum ferritin and serum caeruloplasmin levels were in the normal ranges. Other infective aetiologies like hepatitis B virus (HBV), hepatitis C virus (HCV), leptospirosis and scrub typhus were ruled out with their respective diagnostic tests. ELISA test for detection of immunoglobulin M antibodies to hepatitis A virus was done and results were still positive. His liver function tests started to deteriorate further (Table 1)

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Table 1: ***Table depicting trend of liver enzymes***

Day of admission	Serum ALT (U/L)	Serum AST (U/L)	TSB (mg/dl)	Serum ALP (IU/L)	Total serum protein (g/dl)	Serum albumin (g/dl)	Serum globulin (g/dl)
1	79	138	8.1	316	9.3	4.0	5.3
3	112	156	4.4	386	8.0	3.5	4.5
6	234	280	3.8	364	8.0	3.6	4.4
7	286	332	2.8	200	7.8	3.6	4.2
10	270	304	2.2	165	6.7	4.0	2.7
13	265	280	1.9	123	6.0	4.2	1.8
15	118	210	1.5	107	8.5	4.4	4.1
18	102	140	0.9	99	8.6	4.6	4.0

ALT: alanine transaminase, AST: aspartate transaminase, TSB: total serum bilirubin, ALP: alkaline phosphatase,

Suspecting another aetiology affecting the liver, autoantibody panel of AIH was sent which showed positive ANA, positive perinuclear-anti-neutrophil cytoplasmic antibody (p-ANCA), positive anti–SMA with 1:80 titre on indirect immunofluorescence and positive anti-soluble liver antigen (SLA). Immunoglobulin G level was 1684 mg/dL (normal range 600-1660 mg/dL) and anti-LKM antibody was negative. This was suggestive of AIH type I. A fine needle liver biopsy was performed to confirm the diagnosis of AIH. The histopathology (Figure 1) showed occasional hepatocytes with necrosis and arrangement in rosette pattern with scattered lymphoplasmacytic cells in between. Binucleate cells and fatty changes were also observed in a few hepatocytes which were suggestive of AIH.

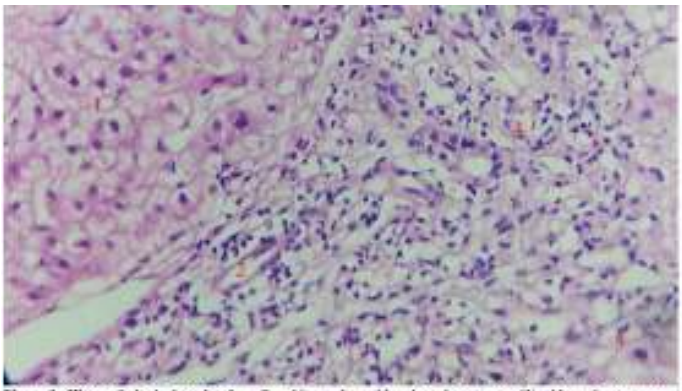

Figure 1: *Histopathological section from liver biopsy shows binucleate hepatocytes (1) with moderate amount of lymphoplasmacytic infiltrate (2) at junction of hepatic lobule and portal tract. Few hepatocytes show fatty changes (3) and few occasional hepatocytes with necrosis and arrangement in rosette pattern (4) with scattered lymphoplasmacytic cells in between, suggestive of autoimmune hepatitis.*

The diagnosis of AIH was established using the simplified criteria given by International Autoimmune Hepatitis Group[6] (Table 2). The score in this patient was 7 which was suggestive of a definitive diagnosis of AIH. He was treated with oral prednisolone 60mg/m^2 for 2 weeks, gradually tapered over the next two weeks, and then continued in a dose of 20mg/m^2. His LFTs were regularly monitored during the treatment and there was improvement in the enzyme level and bilirubin levels as depicted in Figure 2.

Table 2: ***Simplified diagnostic scoring system of the international autoimmune hepatitis group***[6]

Category	Scoring system	Results	Points
Autoantibodies	ANA or SMA	1:40 by IIF	+1
	Anti-LKM1 (alternative to ANA & SMA)	≥1:80 by IIF	+2
	Anti-SLA (alternative to ANA, SMA & LKM1)	≥1:40 by IIF	+2
Immunoglobulins	Immunoglobulin G level	>Upper limit normal (ULN)	+1
		>1.1 times ULN	+2
Histological findings	Interface hepatitis	Compatible features	+1
		Typical features	+2
Viral markers	IgM anti-HAV, HBsAg, HBV DNA, HCV RNA	No viral markers	+2
		Probable diagnosis	≥6
		Definite diagnosis	≥7

ANA: Antinuclear antibody, SMA: smooth muscle antibody, LKM: Liver kidney microsomal antibody, SLA: soluble liver antigen, HBV: hepatitis B virus, HCV: hepatitis C virus, DNA: deoxyribonucleic acid, RNA: ribonucleic acid, HBsAg: hepatitis B surface antigen, IgM: immunoglobulin M, IIF: immunofluorescence

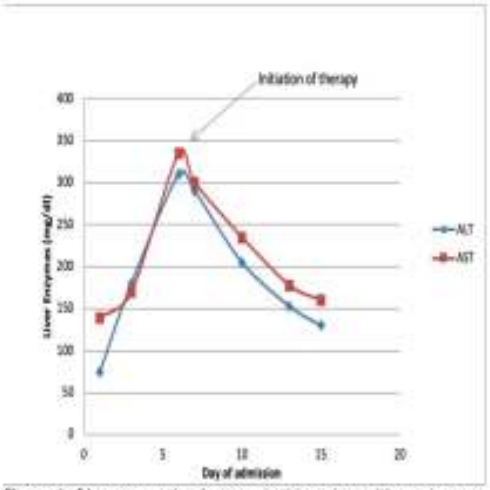

Figure 2: *Liver enzyme level pattern in this patient with autoimmune hepatitis before and after initiation of therapy.*

Patient is being regularly followed up and has shown no signs of steroid toxicity. We have planned to continue the steroid treatment until normalization of the liver enzymes and then gradually tail off.

Discussion

Hepatitis viruses A, B or C can play a role in development of AIH in children and adults[7]. HLA DR13, one of the genetic markers of AIH was found to be associated with liver damage after acute viral hepatitis A[8]. T regulatory cells regulate the immune response by its immunoregulatory action, preventing the proliferation and subduing the function of T autoreactive cells. This response is hampered in AIH[9].

Similar to our case, Huppertz HI, *et al*[10] reported a seven-year boy who was diagnosed as acute viral hepatitis and discharged on resolution of complaints and improvement in biochemical parameters. Six weeks after, he presented with the same complaints, and was then diagnosed as a case of AIH based on autoantibodies and liver biopsy. Vento ST, *et al*[11] studied 58 first- and second-degree relatives of 13 patients of acute hepatitis A to determine whether AIH occurs in patients who are genetically predilected to a defect in asialoglycoprotein receptor defect, triggered by an unknown factor like a virus or a drug. They concluded that the autoimmune response mediated by these antibodies is manifested because viral hepatitis A infection causes a defect in suppressor inducer T cells. Thus, there is a complicated relationship between acute viral hepatitis A and development of AIH. Whether hepatitis A infection triggers the development of AIH or exacerbates an already existing asymptomatic AIH still remains a matter of debate.

AIH may be asymptomatic in 25 to 34% of patients or it may present as fulminant hepatitis[6]. The characteristic biochemical parameters in AIH are the presence of serum autoantibodies, antinuclear antibodies and anti-smooth muscle antibodies in type I and anti-liver kidney microsomal I/III antibodies and anti-liver cytosol antibodies in type II AIH, hypogammaglobinaemia and elevated levels of immunoglobulin G[6]. The titres of these autoantibodies not only help in making the diagnosis but also in monitoring the disease course. Liver histology also plays a major role in the diagnostic work up where piecemeal necrosis, rosetting of hepatocytes and periportal inflammation are a few clues for the diagnosis[12].

Conclusion

Hepatitis A viral infection can be a trigger to develop AIH or exacerbate already existing asymptomatic AIH. Therefore, children with acute viral hepatitis A infection should be regularly followed up and if they present with another similar episode, AIH should be kept in mind as the early initiation of treatment can significantly reduce the morbidity and mortality

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