CASE REPORT

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Use of Steroids for Symptomatic Relief in Hepatitis A Virus-induced Cholestasis: A Case Series

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Abstract

Aim: We aimed to emphasize the potential role of steroids in hepatitis A virus infection (HAV) associated prolonged cholestatic jaundice in this case series.

Background: Viral hepatitis is a significant healthcare burden in India. Hepatitis A and E virus infection are transmitted mainly through the faecal-oral route and are responsible for the epidemic and sporadic cases of acute viral hepatitis (AVH). In recent years changing trends in exposure to HAV are being observed with more cases being reported in adults than before. Though most of the cases with Hepatitis A resolve spontaneously, yet prolonged cholestasis had been reported in <1% of cases. Previous data had suggested the use of steroids in reducing cholestasis. In this case-series, we present our experience of steroids in HAV-associated prolonged cholestatic jaundice.

Results: We had three young patients of HAV infection presenting with cholestatic features of more than 1 month duration. Inspite of all conventional therapies including ursodeoxycholic acid, L-ornithine L-aspartate, anti-histaminics, patients were not relieved of their symptoms. One patient had an episode of per rectal bleed secondary to coagulopathy as reflected by increased INR. After ruling-out other viral hepatitis (HBsAg, Anti HCV antibodies, IgM Anti HEV Ab for Hepatitis B,C and E respectively), all patients were given steroids (40 mg Prednisolone) till bilirubin levels fell <50% of its baseline levels and then steroids were rapidly tapered off. Patients had dramatic response to steroids with sharp fall in direct bilirunbin levels and marked improvement in cholestatic features within 5 - 10 days. All patients had complete resolution of their symptoms with normalisation of bilirubin levels on follow-up after 2 weeks.

Conclusion: Steroids can be used for alleviation of HAV-induced prolonged cholestasis in selected patients after ruling-out other causes of viral hepatitis or reinfection with HAV.

Clinical significance: Judicious use of steroids in prolonged cholestasis due to hepatitis A can be explored as a promising therapy for relief of cholestatic features.

Key words: Hepatitis A, cholestasis, steroids, multidrug-resistance associated protein 2, case series.

Background

Viral hepatitis is a significant healthcare burden in India. Approximately 400 million people all over the world have chronic hepatitis and the Asia-Pacific region constitutes the epicentre of this epidemic. It is equated as a threat comparable to the "big three" communicable diseases – Human immunodeficiency virus, malaria and tuberculosis[1]. Hepatitis A and E virus infection are transmitted mainly through the faecal-oral route and are responsible for the epidemic as well sporadic cases of acute viral hepatitis (AVH). Though HEV has been the leading cause of epidemics and sporadic acute and fulminant hepatitis among adults, in recent years changing trends in exposure to HAV are being increasingly reported[2].

Most cases of Hepatitis A resolve spontaneously with case fatality rate being approximately 0.3% in young adults. Prolonged cholestasis complicates <1% of cases and is associated with morbidity. Previous data suggests use of steroids for reducing cholestasis; however risks associated with the use of steroids hamper its use in patients. In this case-series, we present our experience of steroids in HAV-associated prolonged cholestatic jaundice.

Case 1

A 20-year-old male presented with complaints of gradually progressive yellowish discoloration of eyes for the past 2 months with decreased appetite for 1 month. He had clay-coloured stools for 1 month and intractable itching for the last 15 days. There was no history of blood transfusion/ surgery/dental exposure/high-risk behaviour/jaundice in past. There was no family history of prolonged jaundice. He was managed with tablet cetrizine, multivitamins, and

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ursodeoxycholic acid (UDCA) 300 mg tablets thrice daily with no symptomatic relief. No specific investigations relevant to the cause of jaundice were done. At presentation to our center, he was having complaints of significant itching and inability to sleep because of itching. Icterus was present with rest of the general physical examination being normal. On examination, there were no peripheral signs of chronic liver disease (CLD) and no evidence of ascites/hepatic encephalopathy (HE). *Per abdomen* examination revealed non-tender hepatomegaly (3 cm below right costal margin) with no other organomegaly. His liver function tests showed predominantly conjugated hyperbilirubinemia (Table I). As a protocol, we ordered serology for hepatitis viruses (Hepatitis A, B, C and E). Ultrasound abdomen showed hepatomegaly with no evidence of IHBRD. He was continued with the same supportive management with the addition of Calamine lotion, tab Hydroxyzine 25 mg at night and Cholestyramine sachets 4 g thrice daily before meals. His serology for Hepatitis A virus (IgM Anti HAV antibodies) came out to be positive (4.38 U/ml; normal <0.9 U/ml) with the rest of the viral markers being negative. The autoimmune profile (ANA, Anti LKM1, ASMA, IgG) was done and it turned out to be negative. Consequently, a diagnosis of prolonged cholestasis due to hepatitis A was made. The patient was admitted and planned for a challenge of steroids. Prior to that, LFTs were repeated and his SGOT and SGPT were <2 times the normal value which largely negated the possibility of any reinfection with hepatitis A virus/any other ongoing liver injury. His international normalised ratio (INR) was deranged with a value of 2.98. On second day, he had complaints of mild *per rectal* bleed. Consequently, parenteral Vitamin K and fresh frozen plasma (FFP) were given and INR normalised within 3 days with no fresh episodes of bleeding from any site. Later on, Prednisolone 40 mg was started in view of persistent cholestasis. On the 7th day of steroid treatment, the patient started having improvement in itching with a direct fraction of the bilirubin falling <50% of the level compared with that at time of admission (Table I, Fig. 1). The steroids were then rapidly tapered within the next 2 weeks (10 mg every 4th day and then on 12th day 5 mg for 3 days). He continued to have a persistent fall in direct bilirubin levels during this course. After 4 weeks of stoppage of steroids, the patient was asymptomatic with normal LFTs.

Case 2

A 15-year-old male presented with complaints of yellowish discoloration of eyes for the last 2 months, clay-coloured stools, and progressive itching for 1 month. There was no history of blood transfusion/surgery/jaundice/any prolonged jaundice in siblings. The itching was getting bothersome for the patient inspite of the treatment being given outside in the form of tablet UDCA, L ornithine L Aspartate (LOLA) sachets and tablet cetrizine. His Serology for Hepatitis B and C virus was negative. Chronic liver disease (CLD) was ruled-out on the basis of absence of peripheral signs suggestive of CLD, no evidence of ascites, encephalopathy, and USG imaging showing no signs of cirrhosis. On general physical and systemic examination, icterus was the only finding. LFTs showed hyperbilirubinaemia with a predominant conjugated fraction (Table II). The serology for Hepatitis A turned out to

Table I: LFTs in case 1 (before and after addition of steroids).

	16.11.18	09.12.18	09.01.19	Prednisolone Added	12.01.19	16.01.19	23.01.19	30.01.19	22.02.19
S. Bil (T/D)(mg/dl)	10.2/6.5	12.7/8.6	23.9/16.8		19.6/14.2	11.6/7.2	8/4.2	3.5/2	1.1/0.8
SGOT (U/L)	47	61	29		43	25	45	44	44
SGPT (U/L)	53	65	47		54	43	42	32	32
SAP (U/L)	112		271		224	165	134	154	
TP/Alb (g/dl)	7.2/4		7.2/4.6			7/4.2		7.2/4.2	

Table II: LFTs in case 2 (before and after addition of steroids).

	20.12.18	25.01.19	Prdnisolone Added	28.01.19	31.01.19	03.02.19	11.02.19	15.02.19	18.02.19
S. Bil (T/D)(mg/dl)	9.9/8.3	10.5/8.6		9/6.6	8/5.4	4/2.1	3/2	2/1.2	1.2/0.6
SGOT (U/L)	61	43		54	43	56	44	45	32
SGPT (U/L)	156	27		45	36	34	32	24	22
SAP (U/L)	589	576		485	345	372	274	270	302
TP/Alb (g/dl)	8.1/4.2	7.5/3.8		7.3/4		7/4			7/4.5

be positive (Anti HAV Ab: 10.09 U/ml vs Normal: < 0.9 U/ml). A diagnosis of prolonged cholestasis due to hepatitis A was made. He was started on a similar protocol of steroids as the first patient. The direct bilirubin decreased to < 50% of baseline level after 10 days of daily prednisolone 40 mg. Later on, the steroids were tapered off (10 mg every 3rd day) and the patient had normal bilirubin level after 25 days of therapy institution with no recurrence of symptoms at 3 months follow-up.

Case 3

An 18-year-male presented with progressively increasing yellowish discoloration of eyes for the last 1.5 months, and itching for 1 month. There was no history of clay-coloured stools/bleeding from any other site. There was no history of recurrent jaundice/family history of any prolonged jaundice in siblings/blood transfusion/surgery/dental exposure/high-risk behaviour. He was evaluated by a gastroenterologist at another hospital outside for jaundice and found to be IgM Anti HAV antibody positive. The rest of the viral markers were negative. He was being treated symptomatically for jaundice but the onset of itching and its gradual progression was worrisome for the patient. He was started on tablet UDCA 300 mg TDS , LOLA sachets 5 g twice daily, tab Hydroxyzine 25 mg twice daily with no relief. One week later, he was given cholestyramine sachet 4 gm thrice a day before meals and tab ondansetron 4 mg thrice daily with no significant improvement. His ultrasound abdomen showed mild hepatomegaly with a liver size of 17 cm and no other organomegaly/lymphadenopathy. There was no evidence of intrahepatic biliary radical dilatation (IHBRD). He came to us for no relief in his symptoms. The physical examination revealed icterus and scratch marks on extremities – likely due to itching. Systemic examination revealed no abnormality. The biochemical investigation showed persistently increased bilirubin levels with predominantly conjugated hyperbilirubinaemia. There was a decremental trend in aminotransferase levels with the last SGOT and SGPT being 56 and 23 U/L respectively (Table III). Having a good experience with judicious use of steroids in cholestatic hepatitis A virus and the patient profile being similar to the previous cases, Prednisolone was given in a dose of 40 mg and there was a drop of 75% of the direct bilirubin level within 5 days of therapy. Prednisone was tapered off 10 mg every 3 days in the next 10 - 12 days with normalisation of bilirubin levels at end of therapy. At 3 months' follow-up the patient was doing well with no complaints.

Discussion

HAV infection is frequently mild and asymptomatic in childhood. In developing countries, HAV infection is common during childhood, is often subclinical, and confers immunity to a large proportion of the population[3]. Therefore, HAV hepatitis usually occurs in children, and infection in adults is extremely infrequent.

In contrast, in the developed world, lack of exposure to HAV during childhood results in a large non-immune adult population. Due to better sanitation and personal hygiene practices being adopted in our country, adult cases with hepatitis A infection are infrequent nowadays. In adults, HAV infection has been reported to cause more severe liver disease such as cholestatic and relapsing hepatitis, which has a prolonged course[4,5]. Though the mortality due to HAV is extremely low (0.05% - 0.1%), associated intractable itching may be troublesome.

Initially, acute cholestatic hepatitis A was defined as clinical jaundice for at least 12 weeks, with a peak serum bilirubin greater than 10 mg/dl at a time when the serum aspartate aminotransferase level was rapidly declining[6]. However the criterion has been changed with elevated total bilirubin > 5 mg/dl more than 4 weeks as it is not advisable to wait until 12 weeks in view of increased morbidity[7]. Therefore, in the current scenario, any patient having hepatitis A infection and jaundice for more than four weeks, should raise the suspicion about prolonged cholestasis[8]. Classical signs and symptoms of prolonged cholestasis are pruritic skin, fatigue, weight loss, and loose, clay coloured stools. We had the three cases of prolonged cholestatic hepatitis A, one adolescent and 2 adult male patients. All these patients were receiving the best possible symptomatic treatment for cholestasis including UDCA, LOLA, Cetrizine, Hydroxyzine, Ondansetron with no/little relief. In addition,

Table III: LFTs in case 3 (before and after addition of steroids).

	20.01.19	22.02.19	08.03.19	Prednisolone Added	10.03.19	13.03.19	16.03.19	20.03.19	23.03.19
S. Bil (T/D)(mg/dl)	25.7/17.5	27.5/20.9	22.8/18.8		16/8.6	7.2/4.2	6.6/3.6	3.4/1.8	1.5/0.8
SGOT (U/L)	110	143	56		54	44	54	43	32
SGPT (U/L)	147	176	23		44	34	45	33	24
SAP (U/L)	287	205	218		216	143	137	207	187
TP/Alb (g/dl)	6.6/4.8	7.3/4			7/4.2			7/4	7.6/4.2

the other possible causes of cholestatic jaundice, viz., drug-induced and Primary Biliary Cirrhosis (PBC)/Primary Sclerosis Cholangitis (PSC) were also excluded. There was no history of any drug intake which might have caused the cholestasis. PBC was largely ruled-out as all 3 patients were male and age of onset of disease was early as compared to female preponderance and late onset disease (30 - 50 years) in PBC. Moreover, incidence of PBC is much less in our population as compared to the western world. PSC was ruled-out on basis of imaging showing no evidence of intra/extra hepatic biliary ductal dilatation.

In view of persistent symptoms, we planned to give a course of steroids as previously described by various authors[8-11]. Jain *et al*, in a series of 21 patients with prolonged cholestatic hepatitis A randomised eleven patients in ursodeoxycholic acid and prednisolone arm (Group A) vs Ten patients in ursodeoxycholic acid and placebo arm (Group B). Pruritus responded within a mean of 5 days (range 4 - 8 days) and 24 days (range 18 - 45 days) in group A and group B, respectively with anorexia and performance status improvement occurring early in group A. In addition, mean normalisation of serum bilirubin time was much less in group A patients (44 days) than in group B (94 days). The authors concluded that prednisolone resulted in symptomatic relief and a rapid initial drop in serum bilirubin levels followed by a persistent fall with adverse event[10]. Initially we were skeptical about the use of steroids in these cases due to lack of large series/studies available regarding its use and moreover with an inherent risk of flare of any underlying viral hepatitis virus, but we decided to give steroid challenge to these patients. All the three patients were give short course of steroids and they responded dramatically with normalisation of bilirubin and alleviation of all cholestatic features (Fig. 1-3).

Hepatitis A infection is a self-limiting viral illness with a clinical spectrum ranging from anicteric hepatitis, acute hepatitis, cholestatic jaundice lasting 10 weeks or more, Relapsing with 2 or more bouts of acute HAV infection occurring over a 6- to 10-week period to acute liver failure. Cholestasis has been reported in 0.4 - 0.8 % of cases[8]. In hepatitis A, cholestasis is presumed to occur because of the underlying inflammatory process. Endotoxin and pro-inflammatory cytokines like TNF alfa (TNF α) and IL-1 are released from liver and also as systemic response which inhibits mrp 2 (multidrug-resistance associated protein 2), one of the proteins having a role in bilirubin excretion[11]. Secondly, *in vitro* and animal studies on lymphocyte cultures of patients with alcoholic hepatitis and acute viral hepatitis have suggested that cellular or humoral immune phenomena might be involved in the pathogenesis for prolonged cholestasis[12]. The other proposed mechanism is an interruption in the continuity of bile flow secondary to periportal spotty necrosis[13]. The lympholytic action of corticosteroids may be the reason for their efficacy in these cases. In addition, alleviation of cholestasis by stimulating the alternate efflux pathway for bile salts has also been proposed as a possible mechanism.

Our findings add strength to existing data supporting the use of steroids in patients with HAV-related severe pruritus[8-11]. Since we did not estimate any molecular/cytological derangements described as potential mechanism of steroids so we are not in a position to comment about the exact underlying mechanism of these outcomes with steroids.

Conclusion

Prolonged cholestasis due to hepatitis A may be troublesome in a few patients. We suggest that a short course of steroids may be attempted in patients of HAV infection and associated cholestasis with following strategies:

1. Patients with prolonged cholestasis (total bilirubin > 5 mg/dl for more than 4 weeks).
2. Wait till 4 weeks is advised before starting of steroids as most of the patients recover from cholestasis by this time.
3. Prednisolone has to be instituted at a dose of 40 mg/d till direct bilirubin falls to < 50% of its baseline levels and then it should be tapered off over a period of 10 - 14 days, keeping a close watch on the serum bilirubin levels.
4. Steroid should only be advised in settings of no acute infections, after ruling-out other viral hepatitis infections (Hepatitis B, C and E) and reactivation of HAV (evidenced by nearly normal SGOT/SGPT).

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