CASE REPORT

Acute liver failure secondary to Ayurvedic Herbal medication in a child: a case report

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Abstract

Ayurvedic and Herbal medicine induced liver injury is rarely reported in children. The injury can range from mild asymptomatic elevation of liver enzymes to severe presentation with acute liver failure leading to death. The diagnosis is by exclusion and relies on accurate history and clinical examination supported by laboratory investigations. Various causality assessments such as council for international organizations of medical sciences (CIOMS) and Roussel Uclaf Causality Assessment Method (RUCAM) have been reported to be useful in reaching the diagnosis of Herbal Induced Liver Injury (HILI). However, these scales have not been validated specifically for pediatric age group. In this report, we present a case of a child who was presented to our department with acute liver failure after taking unlabeled ayurvedic medicine for jaundice and loss of appetite. The child was examined for age specific causes of hepatic injury and acute liver failure and he was managed conservatively. Despite extensive search, we did not find any etiology and suspected herbal medicine induced hepatic injury. She recovered completely after stopping the offending medicines. This case highlights the paradoxical hepatotoxic effect of such medications, widely considered safe and natural by the masses. Pediatric hepatologists and general practitioners should be well aware about such adverse effects of herbal medications when encountered with patients with abnormal liver functions. The health authorities need to establish strict quality check and regulations both in the production and sale of ayurvedic medications.

Keywords: Drug induced liver injury; liver failure; Ayurvedic, medicines

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INTRODUCTION

Ayurvedicand and Herbal Medicines (AHMs) have been widely used in India for centuries. Most of these preparations are a mixture of different components produced in a crude unregulated method. In contrast to the common notion of their safety, recent studies have shown that these medicines cause severe liver injury including acute liver failure and even death(1,2). These paradoxical hepatotoxic effects of AHM necessitate adequate awareness among healthcare providers as well as general masses.

Like Drug Induced Liver Injury (DILI), AHM liver injury is a diagnosis of exclusion. However, herbal medications often represent a mixture of many phytochemicals, in contrast to DILI which is because of a single chemical(1,3).

We present this unusual case of Acute Liver Failure (ALF) in a child secondary to AHM intake that recovered completely after drug discontinuation.

CASE REPORT

A previously healthy 8 year old girl was suffering from vomiting and abdominal pain for 2 weeks. She developed jaundice associated with high colored urine along with mild fever during this period. She was given an Ayurvedic medication (unlabeled) for jaundice which was self-prescribed. It was given to her twice a day together with water for 15 days. Her symptoms worsened with increasing jaundice then she was taken to a pediatrician. Investigations revealed deranged liver tests (Table). She was referred to our center for the management of acute liver failure.

On examination, she was afebrile, icteric, and pale. However, she was conscious and well-oriented. Her anthropometry was normal for age [Weight 24 Kg, Height 126 cm and BMI 14.6 kg/m^2 (z-score 0 –minus 1)]. Oral examination showed bluish black discoloration of teeth; and eye examination showed no Kayser Fleischer (KF) rings. Abdominal examination revealed hepatomegaly (liver span

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11 cm) with splenomegaly (2 cm below costal margin) and moderate ascites. The remaining systems were unremarkable.

Her initial investigations revealed direct hyperbilirubinemia, transaminitis, and vitamin K1 independent coagulopathy (Table). Complete hemogram, kidney function, total serum Immunoglobulin (IgG) [730 g/L (normal range: 650-1600)], and ammonia were normal. Blood and urine culture were sterile. An ultrasound abdomen showed ascites, normal echogenic liver, and spleen without collateral circulation. Viral serology for Hepatitis A, E, B, and C was negative. Autoantibodies [Anti-nuclear (ANA), anti-smooth muscle (ASMA), anti-Liver Kidney Microsome(LKM), anti-mitochondrial (AMA), and anti-Liver cytosol (LC1)] were negative. Further, serum ceruloplasmin was low [14mg/dL, normal 20-60 mg/dL), and urinary copper was elevated (78.49 mcg/day cut off: 40 µg/24 hours). D-penicillamine challenge (500 mg given 12 hours apart) indicated an increased 24 hour copper excretion in urine (626.54 mcgm/day). Our initial suspicion included Wilson disease, seronegative AIH, and HILI.

Herbal medications were stopped immediately on the day of admission. Empirical broad spectrum antibiotics (Cefotaxim), N-acetylcysteine, and Vitamin K1 (daily parenteral dose/ 3 days) were started. Enteral Lactulose and Rifaximin for gut sterilization were initiated. Oral D-penicillamine and zinc were started with the suspicion of Wilson disease. Liver biochemistry showed gradual improvement; on the 10th day of hospitalization, the ALT level reduced by> 50% of pre-admission value (ALT 643 IU/L) with a notable decrease in total bilirubin and AST levels (Table). However, PT/ INR remained high without bleeding diathesis or evidence of encephalopathy.

Persistent coagulopathy precluded percutaneous liver biopsy; hence, after 3 plasma transfusions, a trans-jugular liver biopsy was performed on the 14thday of hospitalization. It showed confluent necrosis, infiltrate in hepatic lobules and portal tract with interface hepatitis. The infiltrate was consisted of lymphocytes, neutrophils, and few eosinophils, mostly with the absence of plasma cells. Special stains revealed no excess iron and copper stores (Figure). Quantitative copper level was normal (31.8 mcgm/gm dry weight).

With clinical improvement and liver biopsy picture, HILI associated Pediatric Acute Liver Failure (PALF) was suspected and therapy for Wilson disease was stopped. Clinical exome sequence for known metabolic liver diseases was negative. Child was discharged on the 16th day on Ursodeoxycholic acid (UDCA) and was given multivitamins supplements. On follow up, child recovered completely with the normalization of biochemical and radiological parameters over the next 3 months.

DISCUSSION

Acute liver failure in children is defined according to the consensus statement issued by Pediatric acute liver failure (PALF) study group(4). Reports of PALF associated with ayurvedic herbal medications are rare in the literature. A recent report described fatal outcome in individuals with unknown herbal poisoning (5).

Table 1. Relevant laboratory parameters before and during hospitalization and on follow up

Day / Test	Normal	Pre-hospitalisation	Day 1	Day 3	Day 5	Day 6	Day 10	Day 16	6 months, follow up
Bilirubin total (mg/dl)	0.3- 1.2	24.12	23.6	23.3	20.3	20	19.6	16	0.6
Bilirubin direct (mg/dl)	0- 0.2	13.6	16.9	17.0	15.4	15.3	15.5	12.2	0.2
AST (IU/L)	5-40	2070	1650	1054	905	1190	801	270	30
ALT (IU/L)	10-40	1370	984	782	609	655	643	300	29
γ-glutamyl transferase (IU/L)	7-64	29	31	30	25	27	32	58	26
Alkaline phosphatase (IU/L)	145-420	330	262	281	222	217	211	257	284
Albumin (g/dl)	3.5-5.5	3.28	3.3	3.2	3.2	3.3	3.8	4.3	4.3
Prothrombin time (Seconds)	11.7-15	29	46.8	49.8	40.3	38.4	45.2	31.8	12
INR	0.9-1.2	2.8	4.5	4.5	3.6	3.5	4.1	2.9	0.9
Hemoglobin (g/dl)	11-15	12	13.2	-	-	-	-	-	12.2
Leucocyte count (per mm3)	4000-11000	6720	4.96	-	-	-	-	-	5320
Platelet (x 10^3per mm3)	180-400	269	252	-	-	-	-	-	263
Hematocrit (%)	40-42		41.0	-	-	-	-	-	39
ESR (mm/hour)	0-10	-	02	-	-	-	-	-	03
Ammonia (µmol/L)	11-35	-	48	-	-	-	-	-	-
Direct coombs test	Negative	-	Negative	-	-	-	-	-	-

ESR: Erythrocyte sedimentation rate

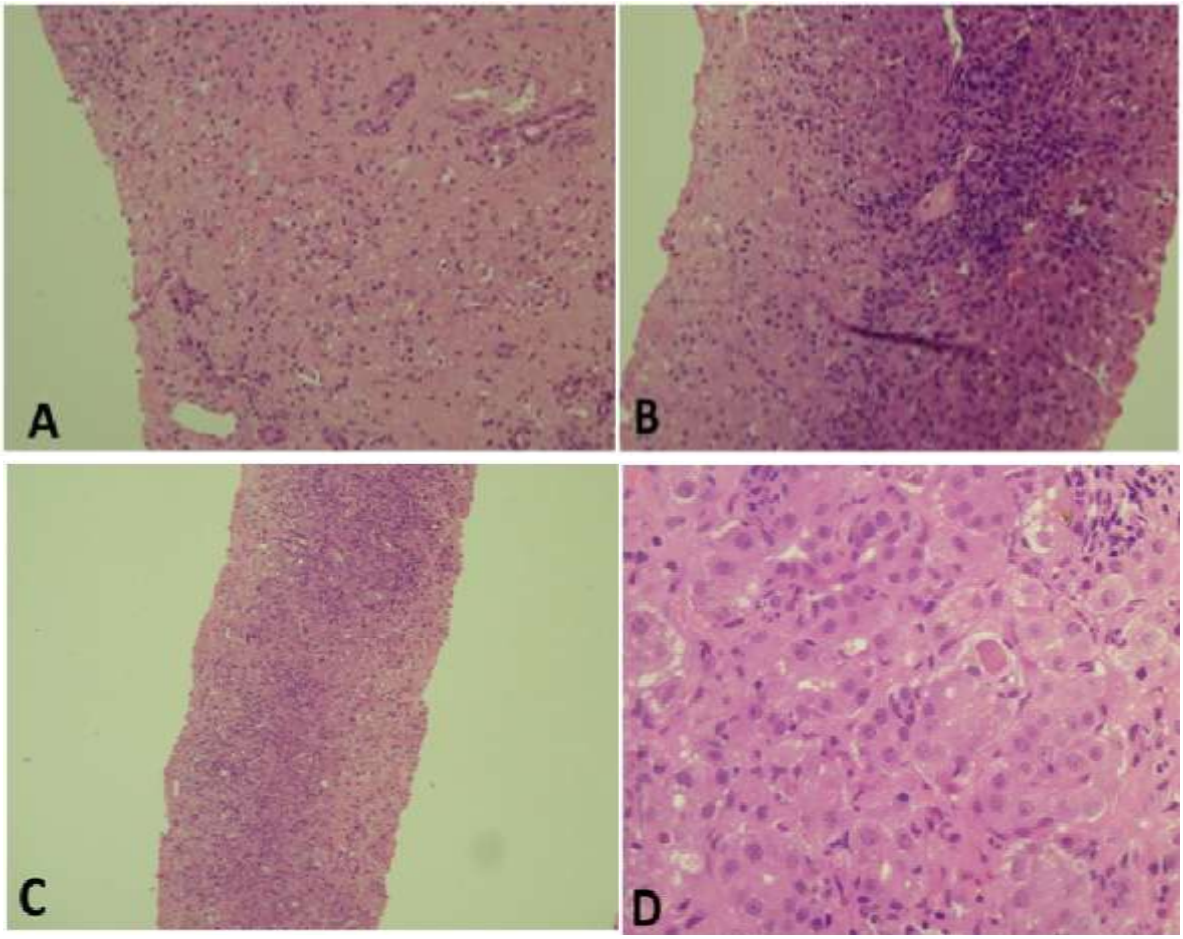

Figure 1. liver biopsy on the 14th day of hospitalization

Ayurvedic and herbal products are responsible for hepatotoxicity in 2% to 11%, and its prevalence in India is reported to be about 1.3%.A study reports higher mortality associated with AHM taken form Unregistered Traditional Healers (UTH).(1) It is concluded that AHM has high levels of heavy metals such as arsenic, mercury, and hepatotoxic volatile organic compounds (hVOC).(1,3)

A recent review pointed to the applicability of modified RUCAM in cases of HILI (6). However, RUCAM score is not applicable to chronic DILI cases or when the onset of the injury is before starting the drug. The most common type of AHM induced liver injury is hepatocellular (1). The R value is defined as serum ALT/upper limit of normal (ULN) divided by serum Alkaline phosphatase/ ULN. It was calculated to be 12.5 in our patient, thus considered an hepatocellular injury (R> 5). An extensive search for common etiologies of PALF was negative in our case. Low serum ceruloplasmin and increased urinary copper excretion suggested Wilson disease, however this confounding laboratory results is known in acute liver failure setting irrespective of the etiology (7).

Chapin et al concluded that liver biopsy in PALF is associated with few major complications and should be considered for early diagnosis and therapy, especially if trans-jugular liver biopsy is available (8). In the context of suspected AHM liver injury, a liver biopsy is useful in ruling out the underlying chronic liver disease, particularly AIH, confirming clinical suspicion of DILI and narrowing the differential diagnosis to a particular drug class (9). In our case, liver histology showed diffuse lobular disarray with hepatocytic ballooning and degeneration along with confluent necrosis. The presence of submassive or massive necrosis correlated with poor outcome in an Indian study. Dense inflammatory cells were present in lobules and portal region with the evidence of interface hepatitis. Interface hepatitis was documented in 70.4% of AHM related injury (1). The measured liver copper content was normal, thus ruling out Wilson disease.

The only treatment for AHM induced liver injury is discontinuation of drug. In cases of severe injury, resulting in acute liver failure, liver transplantation may be needed for survival.

Herb induced liver injury (HILI) was proposed as a probable etiology. This was further supported as what follows: (1) the exacerbation of liver injury and development of PALF after the introduction of the ayurvedic medicine, (2) definite clinical and biochemical improvement after withdrawal of the drugs, (3) hepatotoxicity as a known adverse side-effect of

ayurvedic medicines and (4) histopathologic findings suggestive of possible drug induced damage.

Our patient was given AHM for jaundice and loss of appetite. The cause for this initial liver injury was unidentified and was presumed to be secondary to a hepatotropic virus. A 'multihit' process may explain the severe presentation of liver disease in this case as a result of successive exposure of herbs to already damaged hepatocytes (10). This case highlights the paradoxical effects of AHM which is used as a therapeutic option for liver ailments especially jaundice in India, similar to previous reports (3,11,12). Caregivers may not reveal giving ayurvedic herbal medicines to children, particularly if self-prescribed or by an UTH. A detailed history, clinical examination, and high index of suspicion are needed in order to diagnose this condition especially in children.

Lay Summary

Ayurvedic Herbal Medicine can induce severe liver injury in children. Its prescription and usage in children should be monitored rigorously.

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