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Case Report

Acute liver failure due to Cassia floribunda: case report of three children from a family

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Abstract: Liver is the largest and most vital organ in human body and able to detoxify several chemical compounds. Acute liver failure (ALF) is a rare devastating process that can leads to urgent liver transplantation. It is true incidence in the pediatric population is unknown. The true prevalence of herbal product use and incidence of herbal hepatotoxicity are unknown. Cassia and Senna plants are traditional medicine. Hepatotoxicity of it indicates that, there is a time-lag between herbal intake and hepatotoxicity increase. The real incidence of hepatic symptoms as a complication of herbal remedies has not been identified yet. But it is estimated that the incidence of hepatotoxicity is 0.2-1%.In this study we introduce 3 children of a family with an accidental intoxication of Cassia Floribunda which causes ALF.

Case report: The first case is a four-year-old girl with an icter's complaints and drowsiness after eaten plant in the garden while playing with her sister and friend 3 days ago. 2 days before admission, she suffered from nausea, vomiting and icterus, about 24 hour later malaise, hallucinations and delusions added to patient symptoms,. At the

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beginning her GCS was 10, vital signs were normal, sclera was icteric and pupil has normal size and was reactive to the light. Initial tests showed leukopenia, anemia, and thrombocytopenia, increase of liver enzymes, coagulopathy, and hypoglycemia. With diagnosis, fulminant liver deficiency and hepatic encephalopathy, the patient transferred to PICU and GCS reduced. Her general appearance became better, consciousness increased, lab test findings improved and discharged after 11 days. Second and third cases presented to emergency with similar complaints without icteric, vital signs and other examinations were normal. Initial tests reported reduced platelets, increase liver enzymes, without hypoglycemia. Treatment was started for patient by intravenous ranitidine and monitored in emergency. Two days after discharged. But in third case platelets increased.

Keywords: Acute liver failure, Cassia floribunda, senna, case series

Introduction

Acute liver failure has been originally described as a severe liver injury occurring in a patient without a previous history of liver disease which develops hepatic encephalopathy within 8 weeks of the initial symptoms (1) .

Acute liver failure (ALF) is a rare but potentially devastating process that can leads to urgent liver transplantation. It is true incidence in the pediatric population is unknown, but ALF causes 10–15% of all pediatric liver transplantations (2, 3). (TABLE- 1)

Liver is the largest and most vital organ in human body and able to detoxify several chemical compounds (4). The occurrence of liver toxicity cases linked to herbal medicine raises some concerns regarding herbal safety (5, 6) . According to two reviews, several case reports reported severe hepatic damage associated with botanicals alone or in combination with other medications (5,7). Early identification of the cause of ALF has great importance for different reasons. In some cases, ALF may be controlled with immediate initiation of specific therapies (8) .

Role of plants in ALF:

With historical background on use, the use of herbal medicine can be traced back as far as 2100 BC in ancient China and India (9) . The true prevalence of herbal product use and incidence of herbal hepatotoxicity are unknown. Recently, different hepatic reactions involving botanicals have been documented (10) . The spectrum of liver toxicity includes elevated liver enzymes, acute or chronic hepatitis, cholestasis, hepatic necrosis or fibrosis, cirrhosis, liver failure, and hepatic veno-occlusive disease (10,11) . Some of botanicals that raised severe health concerns are Black cohosh (12) , Chaparral (13) , Saw palmetto (14) , Comfrey (15) , Germander (16) and Kava (17)

TABLE 1. Causes of Acute Liver Failure

Infective	Drugs	Toxins	Metabolic	Autoimmune	Vascular/ischem	Infiltrative
Viral	Dose-dependent	Amanita phalloides (mushroom poisoning)	Galactosemia	Type 1 autoimmune hepatitis	Budd-Chiari syndrome	Leukemia
Viral hepatitis (A, B, B_D, and E)	Acetaminophen	Herbal medicines	Tyrosinemia	Type 2 autoimmune hepatitis	Acute circulatory failure	Lymphoma
Non–A-E hepatitis	Halothane	Carbon tetrachloride (CCl4)	Hereditary fructose intolerance	Giant cell hepatitis with Coomb's positive hemolytic anemia	Heat stroke	Hemophagocytic lymphohistiocytosis
Adenovirus, Epstein-Barr virus, and cytomegalovirus	Idiosyncratic reaction	Yellow phosphorus	Neonatal hemochromatosis		Acute cardiac fai	
Echovirus	isoniazid	Industrial solvents	Niemann-Pick disease type C		Cardiomyopath	
Varicella and measles	Nonsteroidal anti-inflammatory	Chlorobenzenes	Wilson's disease			

	drugs					
Yellow fever	Phenytoin	Hereditary fructose intolerance	Mitochondrial cytopathies			
Rarely Lassa, Ebola, Marburg, dengue, and Toga virus	Sodium valproate	Neonatal hemochromatosis	Congenital disorder of glycosylation			
Bacterial	Carbamazepine	Niemann-Pick disease type C	Acute fatty liver of pregnancy			
Salmonellosis	Ecstasy	Wilson's disease				
Tuberculosis	Troglitazone	Mitochondrial cytopathies				
Septicemia	Antibiotics (penicillin, erythromycin, tetracyclines,	Congenital disorder of glycosylation				
Others	sulfonamides, and quinolones)	Acute fatty liver of pregnancy				
Leptospirosis	Allopurinol					

Malaria	Propylthiouracil Amiodarone					
Bartonella	Ketoconazole					
	Antiretroviral drugs					
	Synergistic drug interactions					
	Isoniazid _ rifampicin					
	Trimethoprim _sulfamethoxazole					
	Barbiturates _ acetaminophen					
	Amoxycillin _ clavulinic acid					

Picture 1, 2 : cassia floribunda

Cassia floribunda

The Cassia species from Fabaceas family grows as shrubs in tropical countries (India, Pakistan, Bangladesh and west China) annually and could grow as weed in wilderness during rainy seasons. There are almost 100 species of this plant (18) .

Senna species plant (Cassia Floribunda) which known as golden showy in English is 2-4 meters height evergreen shrubs with 15-25 cm long leaves, 8-16 pair of 1-2 cm long pinna and pentumerous golden petals which like cluster. Flowering season of this plant is early summer and late fall. [Picture 1, 2]

Cassia and Senna plants are both confirmed in traditional medicine. Cassia plant has been widely distributed in India could achieve a remarkable place in traditional medicine. Some species used as native and traditional drugs for treatment of different diseases (19).

Chemical screening of Cassia juice showed that juice of this plant as like as callus plant, contains glucosides, flavoroids, anthranones and anthracenes derivatives (18).

Performed studies on pharmacokinetics effects of Cassia reported that Senna hydro-alchoholic juice had significant impacts on reducing serum markers (ALKP, Bill, SGOT, SGPT) levels and protecting liver cells hepatocellular damages resulting by paracetamol (20). Anti-inflammatory impact of this plant methanolic juice in comparison with carrageenan, histamine and serotonin had more effects in mouse significantly. One impact of this plant ethanolic juice is fat loss, which causes reducing 42.07% of cholesterol, 6.72% increasing of HDL and 26.84% decreasing of triglyceride (21). other impact of this pant seed methanolic juice is more effective in anti-mutagenic feature in comparison to aflatoxin B1 and more antioxidant activity compare to alfatucophrol (22).

Bakarol is a compound found in different species of Cassia such as Floribunda which has anti-anxiety effects similar to diazepam and could amend sleep quality (23).

The Senna species of Cassia plant is one of the popular plot plant species which used as an strong pesticide in organic farms. Other uses of this plant includes, treatment of childhood teething, fever and constipation with boiled leaves and fungal infections and snails with dried root. It has been used as tonic, antipyretic and stimulant in many countries. Its root and leaves are used as a laxative in Asia (18). Utilization of plant medical properties in preventing and treating of disease goes back to thousands years ago, nowadays traditional medicine systems are still confident in essential role of herbal medicine the health care (24-27).

Considering on abundant use of Cassia plant and increasing interest of public to herbal supplements for treatment of diseases, equally side effects of these compounds have been increased. Potential hepatotoxicity of herbal medicines such as Cassia indicates that, there is a time-lag between herbal intake and hepatotoxicity increase. The real incidence of hepatic symptoms as a complication of herbal remedies has not been identified yet. But it is estimated that the incidence of hepatotoxicity in China is 0.2-1%. (Especially in self-healing cases)(23) .

Iran's traditional medicine includes a wide range of pharmaceutical experiences used to prevent, diagnosis and treatment of liver disorders. Liver is one of the important organs of human body and could amend other organs function. In Iranian traditional medicine Cassia is known as a liver enhancer. However this plant has protective effects versus hepatic cells fibrosis and liver damages in rats (24).

In this study we introduce 3 children of a family with an accidental intoxication of Cassia Floribunda which causes ALF.

Case report:

CASE 1:

A 4 years old girl admitted into emergency room with icterus and drowsiness complaints. Patient had eaten plant in the garden while playing with her sister and friend 3 days ago. From 2 days before admission, she suffered from nausea, vomiting and icterus, about 24 hour later malaise, hallucinations and delusions added to patient symptoms, as she scotching her face and biting her hands, gradually patient became drowsy and her consciousness level decreased progressively. At the beginning her GCS was 10, vital signs were normal, sclera was icteric and pupil has normal size and was reactive to the light. Auscultation of heart and lung were normal and there isn't any

organomegaly in examination of abdomen.

Initial tests showed dropped in cell lines as leukopenia [WBC: 2400] and anemia [Hb: 9.5] and thrombocytopenia [PLT: 83000] increase of liver enzymes [AST: 2179, ALT: 2638, total Bill: 6.7, direct Bill: 4.8], coagulopathy [PT: 31, PTT: 40, INR: 40], hypoglycemia [BS: 51]. The eaten plant identified as Cassia or Sennna Floribunda by the botanical lab equipment.

Regarding to diagnosis of fulminant liver deficiency and hepatic encephalopathy, the patient transferred to PICU. Conservative treatment control of fluids and electrolytes was done, antibiotic therapy started with cefotaxime and amikacin. During first 24hr in PICU, Consciousness decreased and GCS reduced about 6. But from second day her general appearance became better and consciousness increased and lab test findings improved as AST reached 55 in 6 days, ALT:75 in 10 days, Bill total: 2.5 and direct: 2 in 8 days. Coagulation indexes were PTT: 47, PT: 13.4, INR: 1 after 8 days. 2 days after admission WBC: 5400, Hb: 9.4, PLT: 133000 reported. Patient discharged with complete recovery of general appearance and normal tests and full awareness after 11 days.

CASE 2:

Older sister of first case presented to emergency with similar complaints but milder. 5 years old girl admitted with nausea and vomiting. This child had eaten the same plant (Cassia or Senna Floribunda) while playing with her sister and other kid in the garden 2 days ago and after that involve nausea and vomiting 3-4 times per day containing food and none biliary compounds, without diarrhea, patient was alert, not icteric, vital signs and other examinations were normal.

Initial tests reported reduced platelets (22000) but normal WBC (7000), increase liver enzymes (AST: 212, ALT: 246) coagulation factors PT: 20, PTT>60, INR: 2. without hypoglycemia and normal bilirubin (total: 0.4, direct: 0.3). Conservative treatment was started for patient by controlling vomiting through prescribing intravenous ranitidine. The kid was followed and monitored in emergency and feeding was began controlling symptoms gradually. Two days after hospitalization patient discharged, GA was good and examinations were normal. Platelets increased to 30000 and coagulation factor corrected (PT: 14, PTT: 39, INR: 1.1) and liver enzymes reduced (AST: 114, ALT: 180).

Case 3:

Third case is playmate of two mentioned kids whom presented 7 days after eating that plant. In test which performed through her parents request. Thrombocytopenia (PLT: 76000) and liver enzymes increase (ALT: 176,

AST: 151) were reported. WBC, Hb, Bill were normal and no coagulation disorder was reported. The kid hadn't clinical symptoms and examinations were normal. 2 days later the tests were reported; platelets increased into 113000 and liver enzymes decreased. (ALT: 73, AST: 96).

Discussion

The Pediatric ALF study group (PALF study group), created a database of children with ALF. Based on this data, definition of ALF in Patients from birth through to 18 years were included if they met the following criteria:

• Children with no evidence of chronic liver disease;

• Biochemical evidence of acute liver injury;

• Hepatic-based coagulopathy defined as: a prothrombin time more than 15 s or international normalized ratio (INR) more than 1.5 not corrected by vitamin K in the presence of hepatic encephalopathy, or a prothrombin time more than 20 s or INR more than 2 regardless of the presence or absence of clinical hepatic encephalopathy (28, 29) .

The causes of ALF can be schematically grouped into six categories: metabolic, infective, toxic, autoimmune, vascular and malignancy-induced ALF (29, 30). However, the cause remains indeterminate in 18–47% of cases (31, 32).

In neonates and infants, metabolic diseases are the main cause of ALF, for which specific medical therapies may in some instances preclude the need for liver transplantation (1, 8). In older children, viruses (especially hepatitis A virus), drug-induced hepatotoxicity and autoimmune hepatitis are the most common identified causes of ALF, but the cause of ALF still remains undetermined in a large proportion of children (28) .

Severe liver injury has been observed following the consumption of several plant preparations. Many herbal medications have been shown to cause DILI (drug induced liver injury), though the diagnosis is difficult because herbal use is often not elicited in the history. Up to 10% of DILI cases may be due to herbal medications. Commonly available herbal products include comfrey, bush teas, germander, chaparral, mistletoe, kava kava, jin bu huan, ma-huang, and syosaikoto. Comfrey, bush teas, and other plant pyrrolizidine alkaloids damage hepatic vein endothelial cells, leading to sinusoidal dysfunction and veno-occlusive disorder.

Examples of herbal remedies associated with liver failure include pyrrolizidine alkaloids, germander, Chinese herbal medicine, ma huang, chaparral, black cohosh root, pennyroyal, and kava (33) .

Ingestion of the Amanita mushroom is clearly traced to ALF.

Liver injury caused by drugs, herbals, or toxins other than acetaminophen was identified in less than 3% of cases in the Pediatric Acute Liver Failure Study Group registry, the vast majority occurring in children over 10 years of age (28) .

Botanical-induced hepatotoxicity and liver abnormalities have been extensively documented. Many herbal remedies have been recognized as toxins that cause mild or severe liver damage and some have fatal outcomes.

The diagnosis of hepatotoxic liver injury is based upon the interval between drug ingestion and the onset of symptoms, the known hepatotoxicity of the offending agent, serum drug levels (if available), and liver biopsy findings (34) .

Any exposure to hepatotoxic drugs, chemicals, or herbals should be considered possibly related to the liver injury.

Naturally, occurring liver toxins are rare but do occur. Amatoxins are bicyclic octapeptides found in nine species of Amanita mushrooms. Amatoxins remain intact even after cooking or prolonged storage, have a low median lethal dose ,and the amount present in a single mushroom can be fatal. RNA polymerase II is inhibited by Amatoxins, resulting in global interruption of protein synthesis and cell death (35). Kava is an extract of the Pacific Island plant Piper methysticum.The mechanism of liver injury is uncertain but it is speculated that it inhibits cytokine P450 enzymes or depletes glutathione.Other herbal hepatotoxins that have been associated with liver failure include Margosa oil, Noni juice, Atractylis gummifera, and green tea extract.

Cases of severe hepatic damage associated with Senna are rare. The hepatotoxic effect of Senna can be ascribed to its major constituent, sennosides, which are present in leaves and fruits. Sennosides split to rhein anthron that resemble hepatotoxic danthron (36, 37) . Anthraquinone glycosides also present in senna, which are suspected to cause hepatic diseases as well (37) .

Clinical symptoms vary according to the cause of ALF and the age of the child. In infants or older children, there is usually a prodromal phase of malaise, nausea and anorexia. Most often, jaundice develops subsequently. However, jaundice may not develop (especially when the cause of ALF is a metabolic disease or toxic) and clinical diagnosis of ALF becomes much more difficult. Severe hypoglycemia, which may lead to seizures, is frequently observed (38, 39).

Management of ALF should be performed in a pediatric intensive care

unit within a liver transplantation center, where continuous monitoring and multidisciplinary expertise are available (40, 41) .

Pyrrolizidine alkaloids (Heliotropium, Senecio) consists of important plant toxins inducing liver problems. After ingestion of sennosides, 3–6% of its metabolites are excreted from urine; some excreted via bile. Most of the sennosides (~90%) are excreted in feces as polymers which explain its cathartics characteristics (36) .

As seen in [table 1], in evaluating a patient with ALF multiple etiologic agents are present and Accidental or intentional use of available Plants are a major concern.

In our cases, 3 child from a family developed hepatic injury range from acute liver failure in one case to hepatic dysfunction and hepatitis in two other occurred from ingestion of plant cassia floribunda.

The severity of liver failure in first case lead to deciding about liver transplantation for patient. Due to patient recovery and improvement, Referral for liver transplant was canceled.

Inducing ALF plant, cassia although definitely is not present in routine tables of etiologic agent but based on this report must consider as a cause. There are similar reports appear in the literature. One case of toxic hepatitis has been reported after excessive use of senna in a 26-year-old woman (37) . Her liver function improved within one week after senna discontinuation.

An elevation in liver function tests was observed in a 26-year-old woman who reported drinking an herbal tea containing Senna leaves(42) .

Because this plants are usually grown in the small garden of houses, this reports can be of special importance. Easy access to these can be potentially very dangerous. It seems that information to the relevant organization can help to prevent similar cases.

Conclusion:

Acute liver failure in children is a serious problem that can lead to death or need to liver transplantation. When evaluate the causes of ALF, poisoning due to plants should be kept in mind. Senna species can cause ALF which reported in various case reports. Species Senna or cassia floribunda which Cultivated normally or easily in the garden is a cause of ALF. Identifying Senna floribunda as a cause of ALF can have a role in preventing of disease.

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Authors Contribution

All the authors contributed equally to this manuscript.

Conflicts of Interest

This study had no conflict of interest for the authors.

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