Acute Liver Failure After

DETOX Therapy

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Abstract

Acute liver failure is a critical condition due to severe hepatic impairment in a person who does not have a history of liver disease. We present a 27-year-old woman with a two-week history of weakness, fatigue, jaundice and pruritus, as well as nausea and vomiting. The patient decided to try bioresonance diagnostic and alternative holistic medicine to rid her body of toxins and parasites. She started taking for 1 month 9 products containing about 40 herbal and medicinal ingredients. Around 40 days after the start of this therapy the patient was transferred to our unit due to the prolonged high levels in liver enzymes. Upon admission she has low hemoglobin, total protein, albumin, high CRP, liver enzymes, bilirubin, platelets, disturbed coagulation. All viral and immunological markers were negative.

We assume that in the presented case the main cause for liver disease and cholestasis is herbal (HILI) and / or drug-induced liver damage (DILI). There is no definitely a clear answer how these ingredients damaged the hepatic function. The cause of hepatotoxicity is thought to be due to a genetic polymorphism in the cytochrome P 450 enzymes or in the immune response, a synergistic effect on multiple supplements. The probable mechanism for cholestasis involves compromised activity of Bile acids transporters.

The simultaneous administration of so many substances confuses the detoxifying function of the liver, which can be expected. The natural origin of herbs does not deprive them of chemical structure and interactions.

Keywords: Liver failure, Detox, Herbal supplements, Drug-induced liver injury, HILI

Background

Acute liver failure is a critical condition due to severe hepatic impairment in a person who does not have a history of liver disease.

Its course is rapid with evolution to coagulopathy and encephalopathy. The etiological factors include acute virus infection (Hepatitis A,B, E), alcohol abuse or hepatotoxic drugs.

In recent years, there has been an increase in the incidence of liver failure caused by the use of herbal supplements. (1,2)

Nowadays, people strengthen their health by taking herbal supplements. They believe it is safe, effective and without the possible complications of taking medication.

Besides, patients seldom inform physicians about the use of these herbs because they can easily obtain herbs or supplements anywhere without a doctor's approval or prescription.

It is very difficult for clinicians to identify and diagnose patients with a history of herbal-induced liver damage (HILI).

HILI presents in variable unspecific signs and symptoms with general weakness, gastrointestinal (GI) symptoms (i.e., abdomen distension, abdomen pain or fullness), or typical hepatitis symptoms.

The clinical presentation is very similar to drug-induced liver damage (DILI) or at least shares the same pattern of liver damage, which complicates the differential diagnosis.

Clinical case

We present a 27-year-old woman with a two-week history of weakness, fatigue, jaundice and pruritus, as well as nausea and vomiting.

She has no previous personal or familial history of liver diseases, surgeries, allergies and denied travel outside of Bulgaria. Her social history included no tobacco use, no frequent alcohol consumption, no IV drug use, no acetaminophen use, and no high-risk sexual activity. She was fully vaccinated. Her past medical history was only for Hashimoto's thyroiditis – euthyroid form, diagnosed 6 months ago.

The choice of DETOX

The patient decided to try bioresonance diagnostic and alternative holistic medicine. She received „detox“ (detoxification) therapy, which aims to rid her body of toxins and parasites.

From June 1, 2020 she starts taking for 1 month 9 products containing about 40 herbal and medicinal ingredients (Tables 1):

Zentel:

Ingredients	Daily dose	Period of taking
Albendazole	400 mg	5 days

Multimessenger:

Ingredients	Daily dose	Period of taking
Colostrum	500 mg	30 days

Betain HCL	375 mg	30 days
West American Larch (<i>Larix occidentalis</i>)	333 mg	30 days
Inositol	200 mg	30 days
Beta-glucans	200 mg	30 days
Green tea (<i>Camelia sinensis</i>)	200 mg	30 days
Pomegranate tree (<i>Punica granatum</i>)	200 mg	30 days
Astragale (<i>Astragalus membranaceuse</i>)	70 mg	30 days
Shiitake (<i>Lentinulaedodes</i>)	25 mg	30 days
Dancing mushroom (<i>Grifola frondosa</i>)	25 mg	30 days
Zinc (as Zinc citrate)	15 mg	30 days
Selen (as L-Selenomethionine)	70 mcg	30 days

Acti L-Lysin:

Ingredients	Daily dose	Period of taking
L-Lysin	1800 mg	30 days

ParaDetox:

Ingredients	Daily dose	Period of taking
Juglansnigra L.	480 mg	30 days
Artemisia annua L.	480 mg	30 days
Syzygium aromaticum L.	480 mg	30 days
Zingiber officinale	240 mg	30 days
Thymus vulgaris L.	120 mg	30 days
Foeniculum vulgare	120 mg	30 days
Gentiana lutea L.	120 mg	30 days
Hyssopus officinalis L.	120 mg	30 days
Tabebuia Impetiginosa	120 mg	30 days
Allium sativum L.	72 mg	30 days
Capsicum L.	72 mg	30 days

Symbioflor 1:

Ingredients	Daily dose	Period of taking
Enterococcus faecalis	3x20 drops	30 days

Fortecal:

Ingredients	Daily dose	Period of taking
Bilastine	40 mg	30 days

ArtemisininSOD:

Ingredients	Daily dose	Period of taking
Artemisinin	250 mg	30 days
CurcuWIN turmeric extract		30 days
Quercetin		30 days
Decaffeinated Green Tea 95% extract		30 days
Black Walnut Hull		30 days

Pro 10 Biotics:

Ingredients	Daily dose	Period of taking
Lactobacillus acidophilus	8.00 bCFU/gram	30 days
Lactobacillus casei	6.00 bCFU/gram	30 days
Lactobacillus paracasei	4.00 bCFU/gram	30 days
Lactobacillus plantarum	4.00 bCFU/gram	30 days
Lactobacillus rhamnosus	6.00 bCFU/gram	30 days
Bifidobacterium bifidum	3.00 bCFU/gram	30 days
Bifidobacterium breve	3.00 bCFU/gram	30 days
Bifidobacterium lactis	9.00 bCFU/gram	30 days

Tables 1. Herbal and medicinal ingredients of detox therapy**Adverse events**

- 30 days after the start of detoxification therapy, the patient felt acute stomach pain, followed by fever up to 38 C for the next two days.

- Then the urine darkens, jaundice of the sclera develops and generalized intense jaundice occurs
- She was admitted in Infection disease unit, where tests for hepatitis A, B, C, and E, Epstein–Barr virus, and cytomegalovirus infection were negative.
- The patient was transferred to a surgical unit, where abdominal ultrasound and computed tomography showed acute cholecystitis.
- An endoscopic retrograde cholangiopancreatography and papillotomy were performed with the extraction of 9–10 mm periampullary ductal stone.
- Despite the desobstruction, deterioration of the clinical status and resistance of liver enzymes and bilirubin is observed. (Table 2)

Date	Total Bilirubin $\mu\text{mol/L}$	Direct Bilirubin $\mu\text{mol/L}$	ASAT U/L	ALAT U/L	GGT U/L	ALP U/L
10.07	216	134	260	376	376	618
13.07	234	201	265	283	340	972
16.07	279	240	280	267	390	1242

Table 2. Bilirubin and liver enzymes before and after papillotomy

- On 17.07.2020 due to the prolonged high levels in liver enzymes the patient was transferred to our unit. She was afebrile, with stable hemodynamic, with intensive jaundice and pruritus, her mental status was intact.
- Upon admission the patient has hematemesis, low hemoglobin, total protein, albumin, high CRP, liver enzymes, bilirubin, platelets, disturbed coagulation and bleeding from the papilla and MELD – 24 (Table 3).
- We calculated:

Hgb G/L	Ery $10^{12}/\text{L}$	Hct L/L	WBC $10^9/\text{L}$	Gran $10^9/\text{L}$	Lym $10^9/\text{L}$	Plt $10^9/\text{L}$	MCV fL	MCH pg	CRP mg/L
101	3,7	0,31	7,4	5,5	1,3	543	84	27	95,6
TB $\mu\text{mol/L}$	DB $\mu\text{mol/L}$	ASAT U/L	ALAT U/L	GGT U/L	ALP U/L	TP g/L	Alb g/L	LDH U/L	
310	205	276	293	377	1305	48	29	244	
Amylase U/L	Lypase U/L	Glu mmol/L	Na mmol/L	K mmol/L	Cl mmol/L	Urea mmol/L	Crea $\mu\text{mol/L}$		
60	103	7,2	136	3,8	102	2,4	54		
PT	INR	aPTT	Fbg						
19,4	1,71	29,5	4,02						

Table 3. Clinical Laboratory results from 17.07.2020:

- Replacement and support therapy with blood and fresh frozen plasma transfusions, albumin, terlipressin, antibiotics was performed
- Serological markers including those for autoimmune hepatitis (anti– LKM antibodies, ANA, AMA, ASMA, ANCA, IgA, IgG, IgM) and Wilson's disease (ceruloplasmin) were negative.

Course of the laboratory parameters:

The figures show the dynamics of laboratory parameters:

Figure 1. Monitoring of blood parameters

Figure 2. Monitoring of liver enzymes

Figure 3. Monitoring of protein and bilirubin

- In the course of the treatment an improvement in the general condition and laboratory parameters of the patient was reported and the patient was discharged.

Discussion

We assume that in the presented case the main cause for liver disease and cholestasis is herbal (HILI) and / or drug-induced liver damage (DILI). Thus, impaired coagulation can explain bleeding after papillotomy. Nowadays there is an increase in the usage of herbal and dietary supplements, which are recognized as safe. In reality, in some of these products, there are ingredients, that are not announced (like cortisol, etc.). Most of the herbal supplements contain more than 5 substances, which make it impossible to identify the real causative factor for liver injury.

Most herbal hepatotoxicities cannot be reproduced in experimental animal models. Thus, it is difficult to understand the pathogenetic factors. [5] Modern medical technology is not yet able to provide a highly specific and highly sensitive marker or standardized measurements to accurately diagnose HILI. Clinicians can only diagnose HILI by exclusion.

The cause of hepatotoxicity is thought to be due to a genetic polymorphism in the cytochrome P 450 enzymes or in the immune response, a synergistic effect on multiple supplements. [6]

Cholestasis can also be triggered by herbal supplements. The probable mechanism involves compromised activity of Bile acids (Bas) transporters— most likely bile salt export pump (BSEP) and the multidrug resistance— associated protein (MRP) 2, both exporters of Bas to the bile canaliculi, MRP3 and MRP4— which exports BAs to the sinusoidal blood, and the sodium— taurocholate co— transporting polypeptide (NTCP). [7]

Liver injuries are classified in 3 types: hepatocellular injury, cholestatic and combined. In this case, the liver damage is of combined genesis.

There is no strict criteria for diagnosis of DILI/ HILI. Therefore scales are used for calculation of the probability of drug-induced liver injury. The most widely used is a semi-qualitative Roussel Uclaf Causality Assessment Method of the Council for International Organizations of Medical Sciences (RUCAM/CIOMS) scale. [8] The Council for international medical science Russel Uclaf causality assessment method includes weighted scoring of an event according to 7 distinct domains related to the temporal relationship between exposure to a particular drug and the liver injury (both its onset and course), exclusion of alternative non-drug related. In this case the score is 7, probable causing agent for toxic liver injury (table 4.)

Type of liver injury					Score
Hepatocellular			Cholestatic/mixed		
Time of onset of the event:	First treat 5–90 days	2nd treat 1–15 days	First treat 5–90 days	2nd treat 1–90 days	
	<5 or >90 days	>15 days	<5 or >90 days	< or = 30 days	+2
From drug intake until reaction onset	< or = 15 days	< or = 15 days	< or = 30 days		+1
From drug withdrawal until reaction onset					
Course of the reaction					
	>50% improvement 8 days.				+3
	>50% improvement 30 days				+2
	>50% improvement 180 d				+1
	Lack of information or no improvement 180 d				0
	Worsening or <50% improvement 30 days				-1
	Lack of information or no improvement				-1
Risk Factors	Alcohol		Alcohol or pregnancy		+1
	Age > or = 55 years		Age > or = 55 years		+1
Concomitant therapy					-3 to 0
Exclusion of non-drug related causes	All non-drug causes reasonably ruled out				+2
Previous information on hepatotoxicity	Reaction published but unlabelled				+1
Re-challenge	0				-2 to +3
Results: > 8 points definite; 6–8 points probable; 3–5 points possible; 1–2 points unlikely; < 0 points excluded					

Table 4. RUCAM/CIOMS scale for calculation of the probability of drug-induced liver injury in our case

We present a literature reference in LiverTox for 3 of the herbal supplements and medicines used by our patient:

Green Tea is produced from the leaves of the Chinese tea tree *Camellia sinensis*. Usually the drink made from Green tea doesn't have effect on liver enzymes and doesn't induce liver injury. The Green tea is listed in more than 100 herbal preparations. Liver injury from such supplements arises within 3 months. The latent period is from 10 days to 7 months. Most of the patients recovered shortly after the cut off from taking

the drug. The clinical picture consists of acute hepatitis– like syndrome, hepatocellular pattern of serum enzyme elevations, jaundice, encephalopathy, prolongation of INR, depressed albumin production. [8] An article from 2013 published in Drug. Metab. Pharmacokinet. reported that the Green Tea catechins cause clinically relevant inhibition of substrates CYP2B6 and CYP2C8 in addition to CYP3A. [9]

Albendazole is an antihelmintic agent used in treatment of echinococcosis. Common side effect of the drug is mild and transient serum enzymes elevations (in up to 50% of patients receiving the drug for more than few weeks) and in rare cases– acute liver injury. There are reports, that receiving Albendazol for 1–3 days can also lead to liver injury. The mechanism of injury is still unknown, but it is speculated that is due to hypersensitivity. [10,11]

Artemisinin has been used against malaria. Its usage has been associated with self– limiting low rate serum aminotransferase elevations. There has been reports of liver injuries in patients, receiving other antimalarial agents. The onset was within few days to weeks. The mechanism of injury is unknown. There are speculation about idiosyncratic immunological reaction to a hepatic metabolite. The main metabolism of Artemisinin is by the liver, especially via CYP 3A4. [12,13]

Conclusion

This case illustrates several phenomena. It is a combination of distrust in modern medicine, ignorance and the use of this attitude of a significant part of the population for unjustified profit from health problems. Behind this liver damage are structures or organizations regulated in some way. This type of toxic damage is relatively rare, there is no scientific or empirical argument on the program itself. The simultaneous administration of so many substances confuses the detoxifying function of the liver, which can be expected. The natural origin of herbs does not deprive them of chemical structure and interactions. In addition, their composition is not constant, depending on the soil, time of year, circadian rhythm. Scientific discussion is unnecessary. Let's continue to interrogate the sick in detail.

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