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Paper Accepted*

ISSN Online 2406-0895

Case report / Преглед болесника

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Severe toxic acute liver injury – A case report

Тешко токсично оштећење јетре – приказ болесника

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Received: November 24, 2017
Revised: March 12, 2019
Accepted: March 18, 2019
Online First: April 22, 2019
DOI: https://doi.org/10.2298/SARH171124036M

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SUMMARY

Introduction Toxic liver injury is becoming greater problem in today´s hepatology. Until now, more than 900 drugs, toxins and herbs have been identified that can cause different liver injury. There was no significant research of this problem in Serbia so far. The aim of this study is to present the patient with severe form of acute hepatitis, whose etiology is exclusively toxic.

Case outline A 23-year-old male, from Belgrade, previously healthy, got sick with signs and symptoms that correlated with acute hepatitis. Biochemical analyses pointed to severe form of acute hepatitis with impending hepatocellular failure. The diagnosis of toxic liver injury was set. It was caused by the use of number substances and supplements: ecstasy, whey protein, branched-chain amino acid (BCAA), creatine, high doses of vitamin D, glutamine, and multivitamin complex. He was treated with infusion, gastroprotective, and substitution therapy. During hospitalization, the patient's symptoms disappeared with gradual normalization of biochemical analyses of the liver. When the patient's condition was satisfying, blind percutaneous liver biopsy was performed, pathohistological findings: lobular hepatitis, with no fibrosis, etiology correlates to toxic. After a month and a half since the disease had begun, the patient fully recovered.

Conclusion Increased number of persons with toxic liver injury is being registered in developed countries worldwide. Similar trend can be noted in Serbia as well. By presenting young previously healthy man with the severe form of toxic acute hepatitis and impending liver failure, we are pointing out the significance of this problem. Multidisciplinary approach is needed to reach the most effective solutions.

Keywords: acute hepatitis; toxic liver injury; toxins; supplements

САЖЕТАК

Увод Токсично оштећење јетре представља све већи проблем у савременој хепатологији. До сада је идентификовано више од 900 лекова, биљних производа и суплемената који могу изазвати различита оштећења јетре. У Србији нису вршена значајнија истраживања овог проблема. Циљ рада је да се прикаже пацијент са тешким обликом акутног хепатитиса чија је етиологија искључиво токсична.

Приказ болесника Мушкарац старости 23 године из Београда, претходно здрав, показао је симптоме акутног хепатитиса. Биохемијске анализе су указивале на тежак облик акутног хепатитиса са претећом хепатоцелуларном инсуфицијенцијом. Постављена је дијагноза токсичног оштећења јетре које је настало употребом више различитих супстанци и суплемената: екстазија, протеина сурутке, *BCAA*, креатина, високе дозе витамина Д, глутамина, мултивитаминског комплекса. Лечен је инфузионом, гастропротективном и супституционом терапијом. Током хоспитализације, тегобе су престале, уз постепену нормализацију биохемијских параметара оштећења јетре. Са поправљањем стања урађена је слепа аспирациона биопсија јетре и патохистолошки налаз: лобуларног хепатитиса, без фиброзе, токсичне етиологије. Месец и по дана од почетка болести пацијент се потпуно опоравио.

Закључак Повећање броја особа са токсичним оштећењем јетре се региструје у развијеним земљама широм света. Сличан тренд се последњих година може уочити и у Србији. Приказом младог, претходно здравог мушкарца са тешким обликом акутног хепатитиса са пратећом инсуфицијенцијом јетре насталог употребом различитих токсичних супстанци, се указује на значај ове проблематике. Потребан је мултидисциплинарни приступ у циљу њеног што ефикаснијег решавања.

Кључне речи: акутни хепатитис; токсично оштећење јетре; токсини; суплементи

INTRODUCTION

The liver represents a central metabolic organ included in degradation, metabolism, and excretion of different toxic products. So far, more than 900 drugs, toxins, and herbs were registered that can cause different kinds of liver injury. Toxic damage can affect hepatocytes

or biliary tract, and may present with different clinical and biochemical manifestations. Thus, clinical presentation of toxic liver injury can only have asymptomatic elevations in aminotransferase, then as acute hepatitis of different severity, liver failure, chronic hepatitis, acute and chronic cholangitis, micro and macrovesicular steatosis or vascular damage [1, 2, 3].

Toxic liver injury is most commonly caused by drugs (drug induced liver injury – DILI), herbal products (herb induced liver injury – HILI) or other supplements which can be found in drugstores without prescriptions. This natural or synthetic substances are foreign products for the organism and in most cases have to be metabolized in the liver for degradation and excretion. During this process, different hepatotoxic metabolites can appear which can cause liver injury in sensitive people. There are two main mechanisms of toxic liver injury. The first one is direct (intrinsic), dose-depended, which leads to acute hepatocellular necrosis. The effect of these substances is predictable, and it is expected in all people who consume it, with the possibility of reproducibility. The other mechanism is idiosyncratic, due to immune mediated hypersensitivity or metabolic injury, which occurs after some time, up to a year. It is not easy to predict liver damage made in this way, as it occurs only in certain people who have predisposition, and it is not dose-dependent. During metabolization of these substances, many different intermediate products are being created which are binding to cell proteins forming neoantigens that affects the immune system (sensitization) creating toxic effects. In addition, genetically modified metabolic path can lead to creation of intermediate products, which will then have toxic effect [4]. Still, considering the fact that people usually consume different toxic substances at the same time, both mechanisms are included in the liver injury, and they cannot be discussed separately.

In the last couple of years in developed countries, studies have shown a trend of increased usage of supplements, most commonly for the purpose of bodybuilding, losing

weight, staying fit or "health promotion." Thus, research conducted in the European countries (Finland, Germany, Italy, Romania, Spain, and the United Kingdom) showed that around 20% of people used supplement at least once [5]. Similarly, the data showed that in the USA around $28 billion is spent on supplements every year, while 52% of the general population has been using these products in the 1990–2000 period [6, 7].

This kind of research has not yet been conducted in Serbia, and only individual cases have emphasized the significance of consuming potentially hepatotoxic substances [8, 9]. On the market in the last couple of years, there has been a greater presence of different kind of supplements (for bodybuilding, tension relief, sleep improvement, sexual dysfunction, menopause, varicose veins, weight loss, etc.) without previously being examined for potential hepatotoxicity. After considering these facts, the aim of this paper is to present a young, healthy patient with severe form of acute hepatitis whose etiology has been proven toxic due to different supplements intake.

CASE REPORT

A 23-year old male, a student from Belgrade, single, with no children, was admitted to the Clinic for Infectious and Tropical diseases, Clinical center of Serbia, due to poor appetite, nausea, vomiting, fatigue, fever (up to 38.5°C) and yellowing of the eyes and skin. Problems started in the beginning of December 2016, four days before admission. Firstly, he was examined at the primary health care center and sent to Clinic for Infectious and Tropical diseases under suspicion of acute hepatitis. On hospital admission, he was conscious, oriented, with no signs of hepatic encephalopathy, no fever, with jaundice, clear skin with no spider nevus or palmar erythema. Liver was palpable two centimeters below the right rib cage, while the spleen was not palpable. The rest of the physical examination was normal. Biochemical analysis was typical for acute hepatitis with signs of severe acute liver injury

(SALI): aspartate aminotransferase (AST) 10,606 IU/L, alanine aminotransferase (ALT) 13,862 IU/L, total-value bilirubin (TBil) 63.9 μmol/L, direct bilirubin (DBil) 33.6 μmol/L, gamma-glutamyl transferase (GGT) 120 IU/L, alkaline phosphatase (ALP) 102 IU/L, prothrombin time (PT) 32.4%, international normalized ratio (INR) 2.19. The diagnosis of acute hepatitis was set.

Epidemiological data showed that the patient lived with his parents in comfortable conditions. People he was in contact with did not have similar symptoms, and he did not travel outside of Belgrade in the previous six months. He did not smoke, and he denied the use of alcohol. Concerning psychoactive substances, he occasionally used ecstasy (3, 4 methylenedioxymetamphetamine – MDMA). He denied the use of any other psychoactive substances. He also said that in the last two years he regularly consummated whey protein from the black market, creatine in the last three months, vitamin D in the last three months 1,000 IU daily. He also suggested the use of multivitamins and amino acids in the last three years and omega-3 fatty acids.

In order to determine etiology of acute hepatitis more diagnostic procedures were conducted. Virology tests for primary hepatotropic viruses, like hepatitis A virus (anti-HAV IgM), hepatitis B virus (HBsAg, anti-HBc IgM, HBV DNA), hepatitis C virus (anti-HCV, HCV RNA), hepatitis E virus (anti-HEV IgM) were negative. Tests for infection on potentially hepatotropic viruses, such as Epstein-Barr virus, cytomegalovirus, adenovirus, and herpes simplex virus (IgM-class antibodies measured by the enzyme-linked immunosorbent assay or ELISA) were also negative. Immunological tests for autoimmune diseases were negative and metabolic liver diseases were excluded: Wilson disease (normal copper level in blood and urine, normal level of ceruloplasmin, the absence of Kaiser-Fleischer ring), hemochromatosis (normal blood level of iron, ferritin, and the percent of transferrin saturation), and alpha-1 antitrypsin deficiency. With the repetitive use of

abdominal ultrasound of liver, the bile duct obstruction was excluded, while with the help of the color Doppler, vascular diseases of the liver were excluded too.

The diagnosis of severe toxic acute liver injury caused by the consumption of different kinds of substances was established. He was given therapy: glucose 10% infusion, gastroprotective drugs, and due to decreased synthetic liver function, he got infusions of fresh frozen human plasma and vitamin K injection. Since there was a chance of hepatic encephalopathy development, he was given lactulose perorally, and the restriction in daily ingestion of proteins. In the following days, his condition improved gradually. Soon he stopped vomiting, stopped feeling nauseous, and regained normal appetite. Three days after admission, he stopped having fever and abdominal discomfort. Over the course of the treatment, the patient had normal neurological and mental status and he was sleeping well. Laboratory analyses showed gradual decrease of aminotransferases and bilirubin values, with the increase of prothrombin time (Table 1).

After improvement of the patient's condition and his coagulation status, on the 26th hospital day a blind percutaneous, fine-needle-aspiration biopsy was performed. Pathohistological findings showed: portal spaces were the usual size, some of them were infiltrated with lymphocytes. In the liver parenchyma, there were signs of focal necrosis with light cellular and canalicular cholestasis. Inside the sinusoids, there were slightly multiplied Kupffer cells. Protein binding with copper staining was negative, no tumor cell infiltration. Conclusion of the pathologist: it was the case of lobular hepatitis, without fibrosis, with toxic etiology.

After a month of hospital treatment, the patient was discharged in good general health without any symptoms. Two weeks later, which is a month and a half since the beginning of the disease, all biochemical analyses returned to normal. During that visit, he brought to the hospital a list of some of the substances he had been using: whey protein, creatine

monohydrate, branched-chain amino acid (BCAA), glutamine, vitamin C, vitamin D, and multivitamin. The last visit was conducted six months later, biochemical analyses were normal, and there were no signs of previous liver injury.

DISCUSSION

Toxic liver injury is becoming an increasingly significant problem nowadays. Researches show that herbal and dietary supplements (HDR) are frequently the cause of liver injury. Thus, the research conducted in the USA, which covered the 2004–2013 period revealed increase in liver injuries due to HDR ranging 7–20% [10]. Similar tendency was noticed in the European countries as well [5]. At the same time, in developed countries toxic etiology represents the most common cause of acute liver failure (ALF). There was a research conducted at the health center in Oregon, where toxic etiology caused ALF in up to 70% of the cases [11]. According to the American and European liver transplant registries, about 3,000 cases in Europe and 2,000 in the United States had liver transplantation due to the toxic liver injury during the 10–12 years period [12]. In the previously mentioned study from the United States, the most significant cause of severe liver injury were non-bodybuilding HDS, and they instigated the need for liver transplantation in 13% of cases, and deaths occurred in 4% of cases that used these products [10]. In the Mediterranean countries, as well as in developing countries (such as Serbia), toxic substances as a cause of ALF comes second, right after virus etiology, particularly HBV infection [13].

Our patient had toxic liver injury caused by ingestion of a great number of different potentially hepatotoxic substances. First of all, there was ecstasy, which is an amphetamine, used as a stimulant that can cause liver necrosis. It is considered that liver injury is the result of metabolized ecstasy into reactive metabolites, largely by the hepatic P450 system (CYP 2D6) which then influences the oxidation-reduction processes in the liver. Clinically it can be

manifested differently from the mild damage of liver function, which recovers spontaneously, while ALF that needs liver transplantation. It can also cause liver fibrosis. Severity of liver injury is not in direct correlation with the amount of ingested substance, or with the frequency of intake, which points to idiosyncratic type of reaction. It can also cause fever, which was registered with our patient [14, 15]. He was also using whey protein and creatine, which are known for causing liver injury, especially cholestatic type with expressed jaundice. The exact mechanism of liver injury with these supplements is unknown, especially since it has been shown that whey protein reduces inflammation and portal fibrosis in rats with D-galactosamine-induced hepatitis. Still, studies that analyzed pathohistological findings, came to the conclusion that high doses of these proteins have direct toxic effect, but also prior sensitivity and the role of immune mechanism cannot be excluded [16, 17]. Our patient also used supplement BCAA, which increased their levels (L-leucine, L-valine, L-isoleucine). BCAA is associated with non-alcoholic fatty liver disease and injury, and it is proven that their combination with high fat diet (HFD) in experimental mice leads to increased hepatic apoptosis, and elevated circulation hepatic enzymes [18].

Patient also used high doses of vitamin D. The consequences of this hypervitaminosis are related to calcium metabolism and hypercalcemia, which can be manifested as dehydration, thirst, polyuria, anorexia, nausea, vomiting, constipation, fatigue, bone aches, and muscle cramps. The presence of a receptor for vitamin D in hepatocytes, cholangiocytes, stellate cells, and resident immune cells in the liver was discovered, but it is considered that vitamin D alone cannot cause significant liver injury [19]. Still, our patient used different substances, which lead to liver damage in different mechanisms, so we think that the use of high doses of vitamin D cannot be fully ignored. Our patient was also using glutamine, which was actually a good thing, since it is known that glutamine decreases oxidative stress and inflammatory response in critically ill patients with acute liver injury. In that way, glutamine

can improve prognosis of these patients [20]. It is possible that this contributed a speedy recovery of our patient regardless of the clinical presentation of severe liver damage.

Liver damage was manifested as SALI in our patient, with aminotransferase levels over 10,000 IU/L and PT < 40%. There was a possibility that the patient could have developed ALF, as he had two out of three criteria (INR > 1.5, and the absence of prior liver disease), but there was no development of encephalopathy. Symptomatic and supportive therapies were administrated with suspension of all hepatotoxic substances he had previously been using, and the patient fully recovered. The absence of prior liver disease, as well the age of the patient were certainly good prognostic factors, but the influence of hepatoprotective effect of glutamine cannot be ignored [18].

Urgent hepatic transplantation remains the last therapeutic option in the treatment of patients with toxic hepatic impairment and the development of ALF. Current United Network for Organ Sharing criteria for urgent liver transplant are the following:

1. the patient being 18 or older without pre-existing liver disease;
2. life expectancy less than seven days without liver transplantation;
3. onset of hepatic encephalopathy within eight days of the first symptoms;
4. one of the following criteria: ventilator dependence, requirement for renal replacement therapy or INR > 2.0 [21].

In the end, it is necessary to emphasize that we described a young, previously completely healthy man who had severe liver injury caused exclusively by toxic effects of different substances he had been taking for a longer period. The outcome of the disease was favorable, but given the massiveness of hepatocellular necrosis, which could easily have led to ALF with uncertain outcome, we emphasize the importance of constant possible toxic liver damage warnings with different, seemingly harmless supplements and substances.

ACKNOWLEDGEMENT

The authors wish to thank Prof. Ivan Boričić, MD, from the Institute of Pathology, Belgrade, Serbia, for the histopathological analyses and description of the liver tissues of our patient.

Conflict of interest: None declared.

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Table 1. Values of biochemical analyses during the course of the disease

Biochemical analyses	On admission to the hospital	After three days of treatment	After 10 days of treatment	After 17 days of treatment	After 25 days of treatment
AST (IU/L)	10,606	5,717	2,023	114	28
ALT (IU/L)	13,862	9,978	7,219	1,821	352
Total-value bilirubin (μmol/L)	63.9	52.9	45.5	23.3	14.9
Direct bilirubin (μmol/L)	33.6	26.7	23.2	9.2	6.2
Prothrombin time (%)	32.4	43.3	59.2	104	96
INR	2.19	1.72	1.34	0.98	1.02

AST – aspartate aminotransferase; ALT – alanine aminotransferase; INR – international normalized ratio

