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Herbal hepatotoxicity caused by kratom

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Abstract

The liver is the largest exocrine gland and fulfils various vital functions. Xenobiotic metabolism (including various drugs and pharmacological substances) and detoxication are among the most prominent. During this process, the liver can be damaged. This phenomenon is known as Drug-Induced Liver Injury (DILI) or Herbal-Induced Liver Injury (HILI). If a herbal product is the cause. Our case report summarizs a 62-year-old patient suffering from HILI after kratom ingestion. We suggest differential diagnostic tools that can lead to correct diagnosis. We also propose the RUCAM score as a diagnostic tool which can be used to connect a causative agent with liver injury. Some herbal products, however, can be used as therapeutic modalities (e.g. silymarine). Clinicians should consider the unregulated availability of risk herbal products, such as kratom in differential diagnosis of jaundice. An increase of awareness by healthcare provider and public is urgently needed.

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Abbreviations: AFP: Alpha-Fetoprotein; ALT: Alanine Aminotransferase; ALP: Acaline Phosphatase; AMA: Antimitochondrial Antibodies; ANA: Antinuclear Antibodies; ANCA: Antibodies Against Neutrophil Cytoplasm; anti-LKM: antibodies against Liver and Kidney Microsome; ASMA: Antibodies Against Smooth Muscle; AST: Aspartate Aminotransferase; CEA: Carcinoembryonic Antigen; CMV: Cytomegalovirus; CRP: C-Reactive Protein; GGT: Gamma-Glutamyl Transferase; EBV: Epstein-Barr virus; fT4: free Thyroxin Fraction; HAV/HBV/HCV/HEV: Hepatitis Virus A/B/C/E, HIV: Human Immunodeficiency Virus; HSV: Herpes Simplex Virus; NSE: Neuron Specific Enolase; PSA: Prostatic Specific Antigen; RRR: Rapid Reagin Reaction; RUCAM: Roussel Uclaf Causality Assessment Method; TSH: Thyroid-Stimulating Hormone; VZV: Varicella Zoster Virus.

Introduction

Many xeniobiotics and their metabolites can cause liver injury. Nowadays, herbal products (such as cocaine and kratom) and their consumption have become more and more common in patients suffering from so-called Herbal - Induced Liver Injury (HILI). This toxicity appears in various time delays from herbal ingestion, and its severity can vary from inapparent liver enzymes elevation to acute liver failure manifested by hyperbilirubinaemia, metabolic and synthetic dysfunction and coagulation disorders. Our case report discusses kratom as one of many potentially hepatotoxic herbal products. On the other hand, among thousands of plant species, some substances can be used as therapeutic drugs (e.g. silymarine), whose hepatoprotective characteristics have been known for hundreds of years.

Case presentation

A 62-year-old patient without comorbidities was admitted to our clinic to diagnose the aetiology of icterus that had persisted for two months and was associated with pruritus, dys-

pepsia and exhaustion. He was neither in contact with other patients suffering from viral hepatitis or COVID-19 disease, nor with animals. He did not take any medications. He had not consumed alcohol for 4 years, did not smoke cigarettes, and did not consume mushrooms. During admission, we described icterus, hypocholic stool and dark urine coloured with bilirubin. In biochemical blood examination, we spotted combined hyperbilirubinaemia, elevations of transaminases two times the normal upper values, elevated ferritin with normal iron transferrin saturation (Bi total/conjugated: 67/30 umol/l, AST: 2.10 ukat/l, ALT: 4.66 ukat/l, GGT: 2.91 ukat/l, ALP: 4.5 ukat/l).

Serologic examinations excluded viral hepatitis infecion (negative anti-HAV, anti- HCV, anti-HEV, HBsAg), Treponema pallidum infection and HIV. We found only IgG antibodies against EBV, CMV, VZV and HSV without titter elevations during controls. We concluded these findings as immunity after herpetic viral infections in the past, not as acute hepatitis.

Furthermore we evaluated serum ferritin level (358.23 ug/l, (20-270 ug/l)), and transferrin iron saturation (33.5% (30...50)). Indications for genetic examinations for hemochromatosis are: Ferritin levels above 1000 ug/l, or in northern European populations 300 ug/l with transferrin iron saturation above 50%. Our values excluded suspected hemochromatosis [1].

Physiological ceruloplasmin level 0.45 g/l (0.2-0.6) also did not arouse suspicion for Wilson disease [2]. Haptoglobin level 1.11 g/l (0.3-2) was also in the reference interval, and there was no free haemoglobin either in serum or urine. Combined with physiological erythrocyte, haemoglobin levels 140 g/l (130-180) and erythrocyte count ($4.6x10^{12}$ /l) excluded haemolysis as a cause of hyperbilirubinaemia. Immunoglobulin levels were also physiological, as well as TSH and fT4 and oncomarker levels (AFP, PSA, CA 19-9, CA 72- 4, CEA, CYFRA 21-1, NSE, thymidine - kinase). We did not spot inflammatory processes with negative CRP. Autoantibodies were absent (ANA, AMA, ANCA, anti - LKM, ASMA). Abdominal ultrasonography and MR cholangiopancreatography did not reveal any tumorous or infiltrative process of the liver or biliary ducts or signs of primary biliary cholangitis/ primary sclerosing cholangitis [3,4].

According to all those negative findings, we started to think of liver toxicity. In a focused, detailed medical history, the patient admitted kratom consumption (1 pocket daily equals 5 grams daily) for ten days before icterus onset. He ordered kratom from the online website, which is widely accessible and cannot be well controlled. Therefore, we calculated the R-score (ALT/upper limit ALT ÷ ALP/upper limit ALP), which informs about the phenotype of hepatotoxicity (R under 2: cholestatic phenotype, R 2 - 5: mixed phenotype, R more than 5: hepatocellular damage). Our R-value was 3.4 which represents a mixed phenotype of hepatotoxicity (Table 1). We used the database LiverTox for more information about kratom.

According to the LiverTox database and RUCAM score (the score used to describe the possibility between product ingestion and hepatic toxicity according to multiple criteria), we summarised this relationship as probable. RUCAM score calculator here: https://www.ncbi.nlm.nih.gov/books/NBK548272/) [5].

After cessation of kratom consumption and lifestyle modification, we started a therapeutic trial with silymarine and ursodeoxycholic acid with icterus resolution and liver test improvement.

Table 1: Liver tests 4 and 8 weeks after kratom ingestion.

Laboratory parameter	4 weeks	8 weeks
AST (ukat/l)	2.10	0.53
ALT (ukat/l)	4.66	0.79
GMT (ukat/l)	2.91	0.55
ALP (ukat/l)	4.15	2.77
Total bilirubin (umol/l)	166.9	45
Conjugated bilirubin (umol/l)	88.6	18.8

Discussion

A huge business with herbal and lifestyle dietary products with a high sales increase in the last years, surpassing 11 billion USD per year in USA and 8.8 billion USD in Europe, are main factors for increasing herbal induced-liver toxicity [6,7]. In the USA, alternative medicine supplements have become the second most common cause of drug-induced liver injury [8].

Kratom is becoming increasingly popular in western countries, including the USA because of its effect on adrenergic and opioid receptors, as it exhibits euphoric and psychostimulative effects in humans. It is especially used by the online community to mitigate opioid withdrawal symptoms, self-treat heroin/morphine dependence, and pain relief in patients with chronic pain syndromes [9]. It is sold as a supplement in the form of powder or capsules as a cheaper alternative to buprenorphine (opioid replacement medication) without the need for a prescription [10,11]. It mainly causes cholestatic or mixed types of liver injury, but can lead to severe hepatic failure [8].

In the USA, in the period 2011-2017 there were reported over 1800 calls to the US poison centre due to kratom ingestion [11] and 807 reported cases of adverse effects found by the FDA with 30 deaths in the period 2009-2016 [12,13]. According to the review article from 2020 found on PubMed database (using key words, kratom liver injury“), plenty of sources have identified 26 case reports and abstracts, in addition to 7 cases reported from the Drug- Induced Liver Injury Network, 25 in FDA databases, and 27 in internet user forums up to 2020 [14] plus one case report of a 47- year-old man published in 2023 [8].

Generally, herbal medicine products are difficult to regulate because of the wide range offered on various internet websites worldwide. In the USA, only in 6 states, kratom is illegal and in 8 states, it is legal with age or location restrictions [8]. Herbal supplements also tend to have vague or inaccurate labels especially multicomponent ones or may become contaminated during manufacturing [15,16]. Although worldwide databases of potentially hepatotoxic substances are continuously growing, herbal-induced liver injury is still relatively underdiagnosed.

According to the newest guidelines, a liver biopsy is not necessary to confirm the herbal- induced liver injury. However, it can be helpful in the exclusion of other etiological factors of liver damage. It can differentiate other pathological states if the patient´s clinical and laboratory findings do not improve after omitting the suspected offensive factor [16,17]. All clinicians should be aware of herbal products as a potential etiological factor of hepatotoxicity. If suspected, we should also rule out other potential pathological states [17] as we did in our case report.

Conclusion

Herbal hepatotoxicity becomes a more and more common etiological factor of acute liver damage. The rising offer of online accessible herbal supplements and products is the major contributing eventuality to this trend. A thorough and focused medical history is the cornerstone of correct a diagnostic approach. Our case report shows the differential diagnostic work-up of a patient with liver damage using such medical history and RUCAM score. To prevent such toxicity, we suggest focused medical history in patients who take herbal supplements and educate them about the potential danger of such products. Awareness of national and European state institutes for drug control, European Medicine Agency and policy regulation should be made for sale regulation or prohibition of hazardous herbal products. Awareness of national and European state institute for drug control, European Medicine Agency and policy regulation should be done for sale regulation or prohibition of hazardous herbal products.

References

1. Fitzimons EJ, et al. Diagnosis and therapy of genetic haemochromatosis (review and 2017 update). British Journal of Haematology. 2018; 181: 293-303.
2. Ferenci P, et al. EASL Clinical Practice Guidelines: Wilson's disease. Journal of Hepatology. 2012; 56: 671 - 685.
3. Lohse AW, et al. EASL Clinical Practice Guidelines: Autoimmune hepatitis. Journal of Hepatology. 2015; 63: 971 - 1004.
4. Newsone PN, et al. Guidelines on the management of abnormal liver blood tests. Gut. 2018; 67(1): 6-19.
5. https://www.ncbi.nlm.nih.gov/books/NBK548272/.
6. Statista Research Department. Retail sales forecast of herbal and traditional products in Europe from 2010 to 2020. 2022. https://www.statista.com/statistics/646801/retail-sales-forecast-of-herbal.
7. M Szantova, M Jakabovicova. Risk of contamination of nutritional supplements containing silymarin. Current Clinical Practice. 2022; 2: 39-44.
8. Roma K, et al. Kratom-induced acute liver injury: A case study and the importance of herbal supplement regulation. Journal of Hepatology. 2023; 79: 581-584.
9. Tayabali K, Bolzon Cm Foster P, et al. Kratom: A dangerous player in the opioid crisis. Journal of Community Hospita Internal Medicine Perspectives. 2018; 8: 3:107-110.
10. US Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, MD, on the agency´s scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse. 2018. https://fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm595622.htm.
11. Post S, Spiller HA, Chounthirath T, Smith GA. Kratom exposures reported to United States poison control centers: 2011-2017. Clin. Toxicol (Phila). 2019; 57(10): 847-854.
12. Dea D. Schedules of controlled substances temporary placement of mitragynine and 7- hydroxymitragynine into the schedule. J. Fed.Regist. Document. Citation. 2016; 81.
13. Demick DS, Lee TT, Summers AT, El Mallakh RS. Kratom: A growing substance of abuse in the United States. Ann. Clin. Psychiatry. 2020; 32(4): 275-280.
14. Schimmel J, Dart CR. Kratom (Mitragyna Speciosa) Liver Injury: A Comprehensive Review. Drugs. 2020; 80(3): 263 - 283.
15. Szantova M, Sedlacko J. Drug and herbal hepatotoxicity: An overview of clinical classifications. Vnitřní lékařství. 2018; 64(4): 46 - 55.
16. Fontana RJ, et al. AASLD practice guidance on drug, herbal and dietary supplement- induced liver injury Hepatology. 2023; 77: 1036-1065.
17. Andrade RJ, et al. EASL Clinical Practice Guidelines: Drug-induced liver injury. Journal of Hepatology. 2019; 70: 1222-1261.