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LIVER INJURY CAUSED BY A HERBAL AND DIETARY SUPPLEMENT: A CASE REPORT

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SUMMARY

We present a case of a previously healthy male admitted with acute hepatitis while using a body building supplement. An exhaustive laboratory workup for causes of hepatitis was unrevealing. He responded well to withdrawal of the supplement and a course of corticosteroids.

INTRODUCTION

Herbal and dietary supplements (HDS) are increasingly used in the world. In Kenya, HDS are used for medicinal purposes and to improve self-appearance. It is projected that the Kenyan market for HDS will increase with continuing urbanization.1

Despite the fact that these HDS have been available for some time, the market remains poorly regulated. Data from drug induced liver injury network in the USA suggest that, relative to conventional medication -induced hepatotoxicity, liver injury from HDS may be increasing in frequency over time.2 The bodybuilding HDS are the most commonly implicated class of products causing liver toxicity.2 This case report adds to growing evidence of HDS implicated hepatotoxicity.

CASE REPORT

A 35 year old male presented to a private hospital in Nairobi with a one month history of right upper quadrant pain, jaundice and general malaise. He had no significant past medical history, prior history of liver disease or family history of liver disease. He had a previous history of significant alcohol use averaging about 180g per week but had stopped alcohol consumption 6 months prior to admission. He had not used prescription or over the counter medications in the recent month. He worked as a disc jockey and was an avid weight-lifter who had been taking an amino-acid body building supplement daily for the past one year. He denied use of anabolic steroids.

His physical evaluation showed scleral jaundice but no stigmata of chronic liver disease. His body mass index was 25kg/m2. There was no skin rash and lower extremity enema was absent. Abdominal examination did not reveal tenderness, guarding, organomegaly, or ascites.

The results of initial laboratory tests were: Alanine transaminase 1709 mmol/, Aspartate transaminase 1135 mmol/l, Total bilirubin 306 mmol/l, Direct Bilirubin 231 mmol/l, Gamma glutamyl transferase 308.5 mmol/l, Alkaline phosphatase 1135mmol/l, Protein

67.91 g/dl, Albumin 34.06 g/dl. INR was 1.10. His hematologic, metabolic and renal work-up were normal. Random blood sugar was normal at admission.

The aetiologic work-up revealed: Negative viral serology for Hepatitis B surface antigen and core antibodies, Hepatitis C antibody and viral load, Hepatitis A IgM, Herpes simplex virus IgM, Ebstein BarrVirus IgM and IgG and HIV ; Cytomegalovirus IgM was positive but the CMV viral load was undetectable; Negative autoimmune markers (Antinuclear antibodies, VDRL, anti-liver kidney muscle antibody, anti-mitochondrial antibody, anti-smooth muscle antibody and anti DsDNA); Normal serum globulin levels, elevated serum ferritin levels 1240 g/l, normal transferrin saturation levels and iron levels, normal ceruloplasmin and 24 hour urinary copper levels. Serum IgG4 levels were normal.

CT scan of the abdomen revealed a normal sized liver with patent hepatic artery, hepatic vein, portal vein and normal biliary ducts. The spleen was normal in size and there was no ascites.

Liver biopsy showed lobular and portal based inflammation in keeping with hepatitis. Within the lobules there were eosinophils, plasma cells and scattered lymphocytes. Hepatocyte drop-out focally was noted. There was bilirubinostasis with bile pigment deposition within the hepatocytes. The portal tracts showed a mild to moderate inflammatory cell infiltrate. Native bile ducts were present within individual portal tracts. Steatosis, fibrosis and established cirrhosis were absent.

Subsequent daily liver function tests done indicated continuing liver damage and coagulopathy (Table 1) normalized after withdrawal of steroids and insulin was stopped. Six months post steroid use, the patient remains asymptomatic with normal liver function tests.

Table 1
Serial liver function testing

Date	1/7/15	2/7/15	3/7/15	4/7/15
ALT	1019	1728	1430	1426
AST	1135	2416	1056	1071
ALP	162	249	137	116
GGT	291	113	237	195
Bilirubin –Total	248	124	432	371
Bilirubin-Direct	206	80	322	304
Protein	77	70	81	73
ALBUMIN	38	32.5	40	38
INR	1.37		1.96	1.67

On the basis of exclusion of other etiological causes of liver diseases, a diagnosis of probable HDS induced liver injury was made using the RUCAM criteria. Using the RUCAM criteria the score was 7 indicative of a probable diagnosis of drug induced liver injury (DILI). The patient was initiated on high dose steroids (Prednisone 40mg OD) and Ursodeoxycholic acid (300mg TDS) on 6/07/15. He developed diabetes mellitus which was managed with insulin and dietary measures. Table 2 shows the response to steroid therapy

Table 2
Response to corticosteroid therapy

Date	7/7/15	8/7/15	13/7/15	16/7/15	21/7/15	28/7/15	11/8/15	24/8/15	5/9/15	6/10/15	28/10/15	4/11/16
ALT	1162	872	829	798	422	333	297	308	229	123	42	37
AST	894	456	645	201	107	109	95	146	90	56	29	28
ALP	113	101	122	135	96.9	107	93	133	138	125	135	145
GGT	156	145	239	291	275	238	246	422	397	232	227	254
Bili-rubin -Total	391	328	129	40.6	92	97	22	25	10	12	19	11
Bili-rubin-Direct	312	262	115	30	52	40	19	17	6	6	7	6
ALBU-MIN	33	37	36	37	30	35	41	43	44	35	37	44

DISCUSSION

The Patient was evaluated for the differential diagnostic possibilities of non-drug induced liver diseases. The exhaustive evaluation included testing for serologic markers of viral and autoimmune hepatitis and for metabolic and inherited blood markers, including serum ceruloplasmin, iron studies (serum iron, TIBC, ferritin) and hepatic imaging. The presence of plasma and eosinophils in the lobules following clinical and laboratory improvement of liver function, the steroids were gradually tapered over a period of two months. The blood glucose and portal tracts raised a suspicion of autoimmune hepatitis and a drug induced liver injury. The patient's pre-treatment autoimmune hepatitis score was 8. A score of >10 indicates probable diagnosis. To assess whether the amino acid supplement might be a cause for the hepatitis, the RUCAM (Roussel Uclaf Causality Assessment Method) system was employed. The RUCAM system is a means of assigning points for clinical, biochemical, serologic and radiologic features of liver injury which gives an overall assessment score that reflects the likelihood that the hepatic injury is due to a specific medication. The RUCAM is calculated for each implicated medication, a separate RUCAM score being given for each agent that is considered. The total score consists of points for 8 separate factors in 7 categories that help define the "signature" of the drug induced liver injury. These factors are: (1) time to onset (+1 or +2); (2) course (-2, 0, +1, +2 or +3); (3) risk factors (2 scores: 0 or +1 each); (4) concomitant drugs (0, -1, -2 or -3); (5) non drug causes of liver injury (-3, -2, 0, +1, or +2); (6) previous information on the hepatotoxicity of the drug (0, +1, or +2); and (7) response to the challenge (-2, 0, +1, or +3). The individual points range from -3 to +3 and the total possible score ranges from -9 to +14. The interpretation of the final score is as follows: 0 or less indicates that the drug is "excluded" as a cause; 1 to 2 that it is "unlikely"; 3 to 5 "possible"; 6 to 8 "probable"; and greater than 8, "highly probable"(3).

Using the RUCAM causality criteria the score was 7 which is in keeping with a probable diagnosis of drug induced liver injury.

Prescription and over-the-counter medications, notably anti-microbials, non-steroidal anti-inflammatory agents, and anti-seizure drugs, have traditionally been implicated. Worldwide, individuals are

increasingly turning to practitioners of complementary and alternative medicine. Combined with a large market for a variety of dietary supplements, this trend has driven the soaring demand for herbal remedies and health food supplements. Production of these products is not stringently regulated and they are subject to impurities and non-standardization of ingredient concentrations. Contrary to widespread belief, herbal and dietary supplements are not always safe. Toxicities, including liver injury, are more frequently being recognized. (4)

There are numerous reports of liver injury from bodybuilding products, some shown or suspected to contain anabolic steroids.2 Body building supplements have been shown to elicit a distinctive clinical picture of prolonged jaundice in young men with non-fatal outcomes. It is suggested that there may be a common susceptibility factor or that the products may contain 17-alkyl substituted (anabolic) steroids, which are well known to cause this injury pattern. Alternatively, host susceptibility factors, such as drug-or ingredient-specific genetic determinants of drug disposition may account for the injury.2 Assessing potential HDS hepatotoxicity presents unique challenges. The numerous products that frequently contain multiple ingredients, often with unclear chemical descriptors and variable common names, can confound pinpointing the specific toxic agent. Furthermore, some products may seem quite innocuous, such as multivitamins, making it difficult to conceive of any toxic potential. There are many reports of contamination of herbals with microbials, pharmaceuticals, mycotoxins, and heavy metals. Also, unidentified interactions with medications used concomitantly may be responsible for toxicity, yet are difficult to establish. (2)

The hallmark of treatment of any DILI is withdrawal of the offending medication. Corticosteroid therapy has been proposed as treatment for DILI in the setting of acute liver failure setting, but little evidence advanced to support it, and, unlike alcoholic hepatitis or AIH, no controlled trials of steroid therapy for DILI have been performed.5 Wree et al studied the use of steroids and ursodexycholic acid in 15 patients with DILI. The study established that treatment of DILI with corticosteroids and ursodeoxycholic acid is safe and leads to a rapid decline in transaminases and bilirubin. In their study patients without histological signs of pre-existent liver damage similar to our patient showed the most favourable clinical course. Bilirubin and serum transaminases dropped to <50% of peak values within 2 weeks, and normalized within 4-8 weeks. In contrast, patients with positive autoimmune antibodies (anti-nuclear antibodies and/or soluble liver antigen) and/or histological features of chronic hepatitis (n = 3) exhibited a slower reduction in bilirubin and serum transaminase levels. (6)

Our patient was at risk of developing acute liver failure as evidenced by the rising INR. Though repeat histological assessment was not done, his clinical and laboratory parameters indicated dramatic improvement response to Corticosteroids and Ursodeoxycholic acid. He experienced complete recovery after HDS withdrawal and treatment. In general, outcomes of idiosyncratic DILI are good, with only ~10% reaching the threshold of ALF (coagulopathy and encephalopathy). (5)

CONCLUSION

This case adds to the growing evidence of liver injury due to HDS. Given the current regulatory milieu, the most effective prevention of liver injury by HDS is awareness among consumers and health care practitioners that these products have the capacity to cause hepatotoxicity. On a global level, efforts should be put to harmonize regulation and safety standards of HDS. (4)

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