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## CASE REPORT

## Rare cause of acute hepatitis: a common energy drink

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Accepted 14 October 2016

## SUMMARY

A previously healthy man aged 50 years presented with malaise, anorexia, abdominal pain, nausea, vomiting, generalised jaundice, scleral icterus and dark urine. He was not on any prescription or over-the-counter medications, but reported drinking 4–5 energy drinks daily for 3 weeks prior to presentation. Physical examination revealed jaundice and right upper quadrant abdominal tenderness. Laboratory studies were remarkable for transaminitis and evidence of chronic hepatitis C infection. Ultrasound scan demonstrated an echogenic liver and diffuse gallbladder wall thickening. Liver biopsy showed severe acute hepatitis with bridging necrosis and marked cholestasis. The patient was treated supportively with complete resolution of his symptoms and marked improvement in his laboratory abnormalities. The development of acute hepatitis in this patient was likely secondary to excessive energy drink consumption. Energy drinks as well as other herbal/over-the-counter supplements should be considered by clinicians in the workup of patients with acute hepatitis, particularly once other aetiologies have been excluded.

of malaise, anorexia and worsening abdominal pain, which progressed to nausea, vomiting and scleral icterus. He initially attributed his symptoms to an influenza-like syndrome; however, he became alarmed when he developed dark urine and generalised jaundice. The patient had no known personal or family history of liver disease. He had not seen a primary care provider in years and was on no medications (prescription or over-the-counter) prior to admission. He denied any changes in his diet or use of alcohol, tobacco or illicit drugs, but endorsed drinking 4–5 energy drinks daily for 3 weeks prior to presentation. As a construction worker, he used the supplemental energy drinks to help get through his labour-intensive workday. He did get a tattoo in his 20s, but denied any transfusions of blood products or high-risk sexual behaviour.

On physical examination, the patient had normal vital signs, scleral icterus and jaundice. Abdominal examination was remarkable for right upper quadrant (RUQ) tenderness, but there was no ascites, asterixis, spider angiomas or other signs of chronic liver disease.

## BACKGROUND

Nearly 50% of cases of acute liver failure in the USA are due to drug-induced liver injury (DILI).<sup>1</sup> The list of associated drugs and toxins has significantly expanded with the recognition of dietary and herbal supplements as offending agents. Unfortunately, an increasing number of Americans consume herbal supplements and energy drinks on a daily basis, with the misconception that their 'natural ingredients' must render them harmless.<sup>2</sup> It has been estimated that ~23 000 emergency department visits each year are due to adverse events related to dietary supplements.<sup>2</sup>

As the energy drink market continues to rapidly expand, consumers should be aware of the potential risks of their various ingredients. Vitamins and nutrients, such as niacin, are present in quantities that greatly exceed the recommended daily intake, leading to their high risk for harmful accumulation and toxicity.<sup>3</sup> To the best of our knowledge, only one other case report has previously been published in the literature describing acute hepatitis related to energy drinks;<sup>3</sup> herein, we report the second case. Appreciation of this under-recognised phenomenon in clinical practice will decrease prevalence and potentially fatal delays in discontinuation of the offending agent.

## CASE PRESENTATION

A previously healthy man aged 50 years presented to the emergency department with a 2-week history

## INVESTIGATIONS

Laboratory studies revealed normal renal function, elevated aminotransferases and direct hyperbilirubinaemia (table 1). Serum folate and vitamin B<sub>12</sub> levels exceeded quantifiable limits.

Acetaminophen level was undetectable and urine and plasma toxicology screens were negative. Investigations for infectious aetiology, including hepatitis A, B, C, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and herpes simplex virus, only revealed a positive hepatitis C (HCV) antibody with HCV RNA PCR of 59 592 238 IU/mL. Autoimmune workup revealed a negative serum antinuclear antibody, antimitochondrial antibody, antismooth muscle antibody and anti-liver-kidney microsomal antibody (anti-LKM-1). Serum ceruloplasmin and  $\alpha$ -1-antitrypsin levels were normal. Haemochromatosis DNA mutation testing was negative.

RUQ ultrasound scan demonstrated an echogenic liver without cirrhosis, common bile duct obstruction or gallstones. There was also diffuse gallbladder wall thickening thought to be related to underlying hepatitis. The patient underwent a liver biopsy which revealed severe acute hepatitis with bridging necrosis and marked cholestasis.

## DIFFERENTIAL DIAGNOSIS

While the serum aminotransferases and alkaline phosphatase were elevated on presentation, we



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**To cite:** Harb JN, Taylor ZA, Khullar V, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-216612

# Unusual presentation of more common disease/injury

**Table 1** Laboratory results on admission

Laboratory	Value	Reference range
Aspartate aminotransferase (AST)	1802	<37 U/L
Alanine aminotransferase (ALT)	1203	<41 U/L
Total bilirubin	10.3	<1.0 mg/dL
Direct bilirubin	7.7	<0.2 mg/dL
γ-Glutamyl transferase (GGT)	301	5–61 U/L
Alkaline phosphatase (ALP)	206	35–129 U/L
Albumin	3.4	3.5–5.0 g/dL
International normalised ratio (INR)	1.1	0.9–1.2
Vitamin B <sub>12</sub>	>2000	243–894 pg/mL
Folate	>20	4.4–19.9 ng/mL
Mean corpuscular volume (MCV)	97.4	78–100 μm
Platelet count	190	150–450 thou/μmm
Lipase	62	13–60 U/L
Thyroid-stimulating hormone (TSH)	1.22	0.27–4.2 mIU/L
Creatinine	0.84	0.80–1.20 mg/dL
Urea nitrogen (BUN)	12	6–20 mg/dL

were able to narrow our differential diagnosis to various possible aetiologies of hepatitis based on the predominant hepatocellular pattern of laboratory abnormalities. We then further narrowed our differential to the hepatocellular diseases associated with elevated bilirubin and jaundice, including viral infections (eg, hepatitis A, B, C, D and E, EBV, CMV), toxic (eg, alcohol, drugs, environmental), autoimmune, Wilson disease, ischaemia and congestive hepatopathy.

Though the patient was found to have HCV infection, we did not think HCV was responsible for his acute hepatitis. HCV antibody production has a window period, with serum antibodies undetectable by assay until ~10 weeks after the initial exposure.<sup>4</sup> Being that our patient's symptoms only began 2 weeks prior, his positive serology was not compatible with an acute HCV infection, but was deemed more likely a chronic infection. In the absence of clinical signs of haemodynamic instability, we thought ischaemic hepatic injury to be less likely. Furthermore, ischaemic hepatitis is often accompanied by evidence of other end-organ hypoperfusion, such as renal acute tubular necrosis.<sup>5</sup> Therefore, our patient's normal renal function on presentation did not favour the diagnosis of ischaemic hepatitis.

History and examination also made aetiologies such as alcohol, prescribed medications, illicit drugs, environmental causes and congestive hepatopathy less likely. We excluded other viral causes of hepatitis, autoimmune aetiology and Wilson disease based on laboratory results. Biopsy findings in this case were non-specific and can be seen in drug-induced or toxin-induced hepatitis, and in hepatic injury related to other causes, such as autoimmune hepatitis, Wilson disease, coeliac disease and acute viral hepatitis. Having carefully excluded the alternative processes with similar pathological findings, the diagnosis of acute hepatitis secondary to consumption of energy drinks was rendered.

Incidentally, the patient's high levels of serum folate and vitamin B<sub>12</sub> were also consistent with supplemental intake, likely from energy drink usage as he denied any alternative supplementation. The diagnosis was further supported by consideration of chronological and clinical data. His liver injury was directly subsequent to excessive consumption of energy drinks, and resolved on discontinuation of the product.

**Table 2** Laboratory results throughout hospitalisation

Days since admission	AST (U/L)	ALT (U/L)	Bilirubin (mg/dL)
1	1802	1203	10.3
2	1710	1112	11.5
3	2435	1368	13.4
4	4051	2073	19.3
5	2674	1629	15.7
6	1685	1224	12.0
14	35	90	2.7
18	23	36	2.2
Normal values	(0–37 U/L)	(0–41 U/L)	(0.0–1.0 mg/dL)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

## TREATMENT

Our patient was seen in consultation by hepatology during his hospitalisation. He was treated supportively, and the offending agent was withdrawn. Daily liver functions tests (LFTs) and INR were obtained to ensure that the patient did not develop liver failure (table 2).

## OUTCOME AND FOLLOW-UP

The patient's symptoms resolved by the third day of hospitalisation, though his LFTs continued to uptrend until peaking on hospital day 4 (table 2). He was discharged home on hospital day 6. At the time of discharge, the patient was tolerating a regular diet without malaise, anorexia, abdominal pain, nausea or vomiting. Follow-up with hepatology was arranged for new diagnosis of chronic HCV infection. His transaminitis had completely resolved at 2-week follow-up (table 1).

## DISCUSSION

Nearly 50% of cases of acute liver failure in the USA are due to DILI.<sup>1</sup> The list of associated drugs and toxins has significantly grown as the market for dietary and herbal supplements continues to rapidly expand. Although herbal and dietary supplements have been recognised as potential hepatotoxins, this association is commonly overlooked. To the best of our knowledge, only one other case report has previously documented acute hepatitis from overconsumption of energy drinks.<sup>3</sup> We present a second case of a patient who presented with acute hepatitis secondary to energy drink consumption. In the absence of a rechallenge, the association is probable/likely (according to the WHO-UMC causality categories) as the transaminitis occurred with a reasonable time sequence to the energy drink intake, was unlikely to be attributed to other drugs or concurrent diseases and followed a clinically reasonable response to withdrawal.<sup>6</sup>

Energy drinks contain a mixture of B vitamins and an 'energy blend'.<sup>3</sup> As listed on the manufacturer's label, the energy blend includes taurine, glucuronic acid, malic acid, *N*-acetyl l-tyrosine, l-phenylalanine, caffeine and citicoline. The B vitamins involved include high amounts of vitamin B<sub>12</sub> (cyanocobalamin), B<sub>9</sub> (folic acid), B<sub>6</sub> (pyridoxine) and vitamin B<sub>3</sub> (niacin). Many of these ingredients are present in high concentrations, lending to their risk of accumulation and adverse effects. Although several of the ingredients are known to cause toxicity with overdose, none of their toxicity profiles include hepatotoxicity, except vitamin B<sub>3</sub> (niacin).<sup>3–7</sup> We therefore suspect the development of acute hepatitis in this patient was due to the daily consumption of high quantities of niacin-rich energy beverages.

Niacin hepatotoxicity is believed to be a dose-dependent, direct toxic reaction. It can cause transient, asymptomatic transaminitis in up to 20% of people with doses above 500 mg daily.<sup>7</sup> Our patient's daily intake was ~160–200 mg daily, which is below the threshold expected to cause toxicity, but similar to the previously reported energy drink-associated acute hepatitis (around 300 mg of niacin daily).<sup>3</sup> Hepatotoxicity could be due to some of the other compounds within the beverage, for which there are limited toxicity data. Furthermore, little is known about the interactions between the different components of these beverages. Toxicity is also likely compounded by accumulative effect. Each bottle of his energy drink contained 40 mg of niacin, or 200% of the recommended daily value and he consumed 4–5 bottles daily for more than 21 days straight.

In drug-induced and toxin-induced liver injury, laboratory results may present in a hepatocellular, cholestatic or mixed pattern.<sup>8</sup> Niacin toxicity primarily presents with a hepatocellular pattern; however, cholestatic cases have also been described.<sup>7</sup> Our patient presented with a mixed pattern, having elevated transaminases and significantly elevated direct hyperbilirubinaemia. Interestingly, his AST was elevated, disproportionately greater than the ALT (AST 4051 U/L, ALT 2073) and he denied any acute or chronic alcohol use. This abnormal AST>ALT ratio was similarly present in the previously reported case of energy-drink-related hepatitis.<sup>3</sup>

Liver injury secondary to the consumption of dietary and herbal supplements, though increasingly recognised, remains a diagnostic challenge for clinicians due to the lack of clearly defined diagnostic criteria. Diagnosis primarily requires exclusion of alternative causes. Further suggestive features include lack of liver injury prior to supplement exposure, liver injury following product ingestion and resolution of liver injury on withdrawal of the offending agent.<sup>8</sup> Another diagnostic obstacle that further delays diagnosis is patients' non-disclosure of supplement use either due to reluctance to discuss or failure to recognise supplements as actual medications warranting disclosure. The primary treatment for toxin-mediated liver injury is discontinuation of the offending hepatotoxin and monitoring to ensure the liver tests normalise. Recovery will occur in the majority of patients following withdrawal of the offending agent.<sup>8</sup>

One limitation of our observation as well as the previous similar case is that these reports are only suggestive but not conclusive evidence of a causal relationship; they are meant to increase the awareness of healthcare providers of the possibility of a previously unrecognised association. Based on this case and the previous report, we suggest that patients with pre-existing hepatic disorders should use caution when consuming energy drinks containing niacin. With the increasing popularity of energy drinks, clinicians should also be aware of the potential adverse effects associated with their consumption and inquire about energy drink intake in otherwise healthy adults who present with unexplained acute hepatitis. By alerting physicians to this phenomenon, we hope patients will be educated about

the potential risks of energy drink overconsumption, and thus, many unnecessary liver injuries will be prevented, or at least promptly identified and treated appropriately.

### Learning points

- ▶ Drug-induced and toxin-induced liver injury is a diagnosis of exclusion, and relies on chronological and clinical criteria.
- ▶ Suggestive features of toxin-induced liver injury include lack of liver injury prior to toxin exposure, liver injury following product ingestion, resolution of liver injury following withdrawal of the offending agent and absence of other known possible aetiology.
- ▶ Herbal and dietary supplements, including energy drinks, should be considered in the differential diagnosis in patients presenting with acute liver injury of unknown cause.
- ▶ Patients should be educated about the potential risk of hepatotoxicity with the overconsumption of niacin-rich energy drinks.

**Contributors** The authors JNH, ZAT, VK and MS have contributed sufficiently to the project and have met all criteria to be included as authors. All authors have no relevant financial interest in this manuscript and no activities, affiliations or relationships to disclose. All authors have not published or submitted any related papers from the same study.

**Competing interests** None declared.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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