

Khat (Catha Edulis) as a possible cause of autoimmune hepatitis

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to its potential to cause drug induced liver injury. Five of these patients scored between 10 and 15 points, placing them in the probable group for having autoimmune hepatitis. All of these patients were treated with prednisolone and demonstrated a good response to immunosuppression.

CONCLUSION: One possible cause of hepatotoxicity with khat could be *via* triggering of autoimmune hepatitis in a genetically susceptible individual. Further studies are needed for confirmation.

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Key words: Khat; Autoimmune hepatitis; Drug induced liver injury; Acute hepatitis; Herbs

Core tip: Khat causes hepatotoxicity. One possible mechanism could be by inducing autoimmune hepatitis.

Abstract

AIM: To investigate the potential role of khat in triggering auto immune hepatitis.

METHODS: Patients with a history of khat use and acute hepatitis were identified using the computer database in the hepatology department at the Royal Hallamshire Hospital. They were then assessed for probability of having autoimmune hepatitis using the revised autoimmune hepatitis scoring criteria.

RESULTS: Six patients were identified. All of them had presented with acute hepatitis on a background of khat. All were male and five of these patients were of Somali origin, while one patient was from Yemen. The patients were given points on the modified autoimmune hepatitis score which is based on their liver enzymes, autoimmune screen, exclusion of viral hepatitis alcohol and drugs, immunoglobulin levels and liver histology. The patients were given a score of -4 for khat use due

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INTRODUCTION

Khat (Catha Edulis Celestrae) is an evergreen shrub native to East Africa and Southern Arabia. It is chewed daily by over 20 million people in these countries. Chewing khat is a popular social habit, particularly in young males, that has spread to Yemeni, Somali and East African communities living in the United Kingdom and United States^[1]. The use of khat as a stimulant is increasing primarily due to immigration. The Somali population in the United Kingdom is estimated to be as high as 90000, and

concerns over health and social problems associated with chewing khat have grown due to its potential side effects including hypertension, coronary vasospasm, myocardial infarction, delayed intestinal absorption, and mood disorders, which may result from its sympathomimetic action^[2].

Various studies and case reports have suggested that khat is also hepatotoxic, leading to deranged liver enzymes and also histopathological evidence of acute hepatocellular degeneration^[3-7]. Recent studies in Somali populations have shown that khat can cause acute severe liver injury in humans due to its hepatotoxic effects^[8,9]. Certain drugs that are known to be hepatotoxic cause liver damage by inducing an immunological response leading to a clinical presentation similar to autoimmune hepatitis (AIH). D'Souza *et al*^[10] have described atypical presentation of AIH in young Somali men, although any history of khat use was not reported. Our aim was to assess the possible relationship of khat and autoimmune hepatitis in patients presenting with acute hepatitis on a background of khat use.

MATERIALS AND METHODS

The Hepatology database at Sheffield Hospitals was searched for patients referred to the Hepatology department between 2005 and 2010 with liver problems and a history of khat use. All of the patients were tested for hepatitis A, B and C serology, autoimmune profile (including antinuclear antibodies, smooth muscle antibodies and LKM-1 antibodies), ceruloplasmin, alpha-1 antitrypsin, and serum ferritin, and underwent ultrasound scanning of the abdomen, which was normal. This was followed by a percutaneous liver biopsy. Each biopsy was reviewed with particular attention to features of interface hepatitis, lobular necroinflammation and biliary changes. The patients were categorized according to the probability of having autoimmune hepatitis: no evidence (scores < 10), probable (scores of 10-15) or definite (score of more than 15), according to the established international criteria for diagnosis of autoimmune hepatitis^[11,12].

All patients were treated with prednisolone (0.5 mg per kilogram per day) initially. Complete response, partial response and no response were defined according to the original and revised international autoimmune hepatitis criteria^[11,12].

RESULTS

Acute hepatitis was defined in accordance with the scheme established by the Council for International Organisations of Medical Sciences (CIOMS)^[13], and by the USFDA Drug Hepatotoxicities Steering Committee^[14]. Eight patients were identified, of which six had presented with acute hepatitis on this basis. All were male and five of these patients were of Somali origin, while one patient was from Yemen. The age range of these patients was 24 to 57 years (mean 42.3 years). All of the patients had

been using khat for several years. There was no history of herbal medication (other than khat) or alcohol use in any patient. All other causes of liver injury were excluded *via* non invasive liver screen. Five of the six patients went on to have a liver biopsy. The patients were scored according to the revised autoimmune hepatitis criteria - (Table 1). They were given -4 for khat use on the scoring system due to its potential hepatotoxicity. Despite this, five out of six patients had a pre treatment score of 10 to 15 which placed them in the probable group for autoimmune hepatitis.

The five patients that were in the probable group had at least a partial response to corticosteroids with a greater than 50% reduction in their ALT after one month of treatment. Only two patients had more than 1 year of follow up, with one showing complete response to treatment. The patient that had scored negative for AIH (< 10) showed the least improvement with prednisolone and continued to have raised liver enzymes after 1 year of treatment. Four out of the six patients were maintained on long term low dose prednisolone while the other two patients were lost to follow up after 1 year. Two patients were commenced on azathioprine with complete response at 1 year follow-up. There was no history of re-exposure to khat.

Five out of six patients met the criteria for probable diagnosis of AIH but none of the patients actually met the criteria for confirmed diagnosis (score > 15). It has been reported previously that Somalian patients with AIH present atypically. It is therefore suggested that the AIH in these patients may have been triggered by khat use.

DISCUSSION

Over 40 khat strains are grown and used in Southern Arabia and East Africa. It is consumed in the form of fresh leaves which may often be contaminated with pesticides. The leaves of khat contain the Pyrrolizidine alkaloids, Cathine, Cathidine, and Cathinone. The pleasure derived from khat chewing is attributed to the euphoric action of Cathinone which is a sympathomimetic amine, with properties similar to amphetamine^[15]. Although Cathinone is restricted in the United Kingdom under the Misuse of Drugs Act 1971, khat possession and use are not^[1].

The diagnosis of drug induced liver injury (DILI) *vs* AIH triggered by khat is challenging. Various causality methods have been used for herbal induced liver injury and can be broadly divided into retrospective and prospective methods^[16-25]. Establishing with any degree of certainty as to whether the liver disease is drug-induced can be very difficult^[26]. The issue is further compounded by the relatively rare incidence of DILI, under reporting and potential drug interactions, due to which establishing the identity of the culprit drug may be impossible^[27,28]. Furthermore, histology is often unhelpful as it only provides the type and degree of liver injury rather than the

Table 1 Patient scores according to the revised criteria for diagnosing autoimmune hepatitis

Parameters	Score	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
ALP:ALT (or AST) ratio		125/1569	170/1223	187/1957	179/1005	298/1052	59/118
< 1.5	2	2	2	2	2	2	2
1.5-3.0	0						
> 3.0	-2						
Serum IgG above normal							
> 2.0	3	3		3	3	3	
1.5-2.0	2						2
1.0-1.5	1						
< 1.0	0		0				
ANA, SMA or LKM-1							
> 1:80	3			3		3	
Approximately 1:80	2				2		
Approximately 1:40	1						
< 1:40	0	0	0				0
AMA positive	-4	Negative	Negative	Negative	Negative	Negative	Negative
Viral hepatitis markers							
Positive	-3						
Negative	3	3	3	3	3	3	3
Drug History							
Positive	-4	-4	-4	-4	-4	-4	-4
Negative	1						
Average alcohol intake							
< 25 g/d	2	2	2	2	2	2	2
> 60 g/d	-2						
Liver histology							
Interface hepatitis	3	3	3	3	3	N/A	3
Lymphoplasmacytic infiltrate	1	1	1				1
Rosetting of liver cells	1	1	1	1			1
None of the above	-5						
Biliary changes	-3						
Other changes	-3						
Other autoimmune diseases	2	2 (IDDM)	0	0	0	0	0
Optional additional parameters							
Sero positivity-other antibodies	2					2 (ENA+)	
HLA DR3 or DR4	1	N/A	N/A	N/A	N/A	N/A	N/A
Pretreatment score		13	8	13	11	11	10

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; ANA: Antinuclear antibodies; SMA: Anti-smooth muscle antibody; LKM-1: Anti-liver/kidney microsomal type 1; AMA: Anti-mitochondrial antibodies; N/A: Not available.

aetiology. The key to causality is to assess the temporal relationship between drug initiation and development of abnormal liver tests and to diligently exclude other causes of liver diseases. This includes liver injury induced by alcohol, viral hepatitis (acute hepatitis A, B, C and E), autoimmune causes, metabolic disorders, biliary obstruction and sepsis.

The diagnosis of AIH alone is based on the characteristic clinical and histological features as well as the absence of other potential causes of hepatitis. The revised criteria for diagnosis of autoimmune hepatitis are considered the current gold standard^[11,12]. Drugs can occasionally cause a clinical-serological picture similar to autoimmune hepatitis and may trigger autoimmune hepatitis in patients with an underlying genetic predisposition to autoimmune hepatitis, or the patients may develop AIH as a sequel of the drug itself. In a Swedish study of 23 patients who developed chronic DILI 23.1% were subsequently diagnosed with autoimmune hepatitis, the suspected drugs being ranitidine, enalapril, oestrogen, carbamazepine, and oestriol^[29]. In a recent case series,

Peevers *et al*^[9] described seven patients presenting with acute hepatitis who had a history of khat use. Two of those patients met the criteria for the diagnosis of probable AIH. It has been reported previously that Somalian patients with AIH present atypically. In a study of Somalian patients with a history of AIH, it was noted that all of the patients were male and scored in the probable group^[10]. History of chewing khat was not mentioned in that particular study. However, in our series, all of the patients who presented with acute hepatitis had a history of khat use with five out of six patient meeting the criteria for probable AIH and demonstrating a good clinical response to immunosuppression. We therefore conclude that, in addition to producing DILI, khat may also trigger AIH in patients with a possible genetic pre-disposition.

Recently, Terschké *et al*^[30] have validated the use of the CIOMS scale to be used with herbal induced liver injury (HILI) cases. Although the diagnosis of AIH is well founded in these patients, the causality assessment by means of CIOMS is not available. Also, the small number of patients in this series means that our hypoth-

esis of AIH being induced by khat can only be tentative and should be interpreted with caution. Whether these patients benefit from long-term immunosuppression after stopping khat remains unclear. Further studies of similar groups of patients are required to increase our understanding of this phenomenon and its management.

COMMENTS

Background

Khat is widely used in Southern arabia and East Africa. It is also known that autoimmune hepatitis presents atypically in these population as it is more common in males and presents at a younger age.

Research frontiers

Khat is well known to cause liver damage but the mechanism of this remains elusive. Patients in the areas where khat is consumed, present with atypical autoimmune hepatitis - the cause of which is not known.

Innovations and breakthroughs

The authors present an interesting observation of development of autoimmune hepatitis in a group of patients consuming Khat.

Applications

People can treat these group of patients more effectively by understanding the possible mechanisms of liver damage caused by Khat use.

Terminology

Khat (*Catha Edulis Celestrasae*) is an evergreen shrub native to East Africa and Southern Arabia. It is chewed daily by over 20 million people in these countries for its addictive and euphoric properties.

Peer review

This is an important case-report and the manuscript reads well.

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