



ORIGINAL ARTICLE

TRENDS OF KHAT- RELATED AUTOIMMUNE HEPATITIS IN YEMEN

*¹Alkaff Hamed, O., ²Alrabeei Jamila, A. and ³Al-kaf Ali Gamal

¹Assistant Professor of Internal Medicine and Gastroenterology, Department of Internal Medicine, Faculty of Medicine & Health Sciences, Sana'a University, Yemen

²Consultant of Internal Medicine and Gastroenterology, Department of Internal Medicine, Department of Medicine, Kuwait University Hospital, Sana'a University, Yemen

³Professor of Medicinal Chemistry, Dean of Faculty of Pharmacy, Sana'a University, Yemen

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ABSTRACT

Background/Aims: Khat is a natural stimulant from the *Catha Edulis*' plant that is cultivated in Yemen and most of East African regions. It is widely used in Yemen as a pass time social habit. Chewing of this cursed plant's leaves has been shown to have a direct damaging effect on liver tissue. There are few case reports on the effect of Khat chewing and hepatitis, but this is a retrospective study to investigate this relationship in response to recent case reports from the UK and Australia.

Our Aim: was to show the direct relation between the habit of Khat chewing in the region and autoimmune hepatitis (AIH).

Methods: This is a retrospective study that analyzed 68 patients who were referred to a tertiary teaching hospital in Sana'a, Yemen, from January 2011 to December 2014 who were diagnosed as an acute autoimmune hepatitis based on serum biochemistry, immunoglobulins, autoantibodies and hepatic viral markers. Khat chewing habit was also recorded.

Results: There were 68 patients in this study with mean age of 28.3 years (range: 15-60). Male (M) to female (F) ratio was 4:1. Khat chewers were accounted for 85% of patients. The age distribution showed typical bimodal distribution of type I autoimmune hepatitis. Liver enzymes' tests (ALT and AST) showed more than three fold's increase in 47% of patients. Seventy two percent of patients showed an elevation of Gamma (G)-globulin rate. Antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) were positive in a high number of patients. Liver imaging did not reveal obstructive pathology. About 80% of the patients responded to the conventional medical treatment.

Conclusions: This performed study clearly showed the high prevalence of autoimmune hepatitis among male Khat chewers with a change in the pattern of autoimmune hepatitis from the norms of the international F:M = 4:1 distribution to the F:M = 1:4 ratio. This is a clear index of the possibility of Khat, being a trigger factor of developing clinical and serologic features similar to that of idiopathic autoimmune hepatitis. Thus, public education as well as physician's awareness should be emphasized.

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INTRODUCTION

The Khat plant (*Catha Edulis*) is a natural stimulant which is widely cultivated in Yemen and most of East African regions. Its' leaves contain alkaloids, which are related to amphetamine-like properties such cathine and cathinone, and additionally a considerable amounts of tanins, vitamins, minerals and flavonoids (Nabuzoka, 2000). It is widely used by adult Yemenis often on daily basis or during the weekend.

*Corresponding author: Alkaff Hamed,

Assistant Professor of Internal Medicine and Gastroenterology, Department of Internal Medicine, Faculty of Medicine & Health Sciences, Sana'a University, Yemen.

It has been estimated that up to 80% of Yemenis between the age 16-80 years have chewed Khat on at least one occasion (Nabuzoka, 2000 and Hassan, 2002). The fresh leaves are chewed to attain a state of euphoria and stimulation, and some authors attributed this to the cathinone which is a psychological stimulant (Gunaid, 1995 and Ageely, 2009). It has other hazards on health in addition to its hepatic toxicity. It causes: gastrointestinal, renal, genitourinary and neurological disorders. It also causes oral ulcerations and cancer (Hassan, 2002). Khat can be grown in droughts where other crops have failed and also at high altitudes. Khat is harvested throughout the year. It is planted in different climate and altitude to obtain continuous supply (Luqman, 1976). There are no controlled trials on the adverse effects of it's regular chewing on humans.

In recent years as a result of globalization, its consumption has expanded in many countries like: KSA, UK, USA; and France and even in Malaysia and China. Biochemically, Khat leaves decrease plasma cholesterol, glucose and triglycerides in rabbits (Al-Habori, 2004) and increase plasma alkaline phosphatase and alanine aminotransferase in white rabbits (Al-Mamary, 2002). Histopathological signs of congestion of the central liver veins were observed with acute hepatocellular damage and regeneration. Spleen was not affected. The amount of Khat consumed by the rabbits cannot be evaluated from the details given. The authors reported that in general, the activity and the behavior of the animals were observed to be normal (Al-Mamary, 2002). In a study conducted to see the long term effect of Khat chewing on rabbits, the data presented showed long term (6 months) both biochemical and histopathological data demonstrating signs of *Catha Edulis*' toxicity. The results showed a significant increase in plasma levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) with all levels of the leaves tested and throughout the treatment period (Al-Habori, 2002). Two types of mechanisms were distinguished for: drugs (chemicals) as a potential triggers of liver injury, which supposes a self-perpetuating liver disease, and the more recognized immune-mediated drug-induced liver injury, which is an acute or chronic process depending of the duration of the exposure of the liver to the hepatic insult (herbal remedies, drugs and chemicals; including the pesticides which are used routinely in the cultivation) and disappears or becomes quiescent when the exposure to one of these factors is withdrawn (Johnson, 1993 and Alhaddad, 2016). Various lessons are derived from immune-toxicological investigations regarding mechanism of induction, heterogeneity of chemicals involved, humeral versus cellular immune response and genetic predisposition to chemically induced autoimmunity are present (Corsini, 2008). Autoimmune hepatitis is a form of liver inflammation, having been first described by Waldenstrom in 1950. It occurs when the body's immune system attacks its own liver cell (Waldenstrom *et al.*, 1950). Although mechanism is not well understood, it is speculated that the exposure to like the above mentioned insults may trigger the disease in people who are genetically predisposed. The condition mostly affects women (female to male ratio is 4:1), majority are between the ages 15-40 years. However, it may affect people of any age or ethnicity (Alvarez, 1999).

MATERIALS AND METHODS

This is a retrospective study from January 2011 to December 2014 of all symptomatic cases admitted to Sana'a University Hospital with a picture of acute hepatitis. After excluding the other known causes of hepatitis, especially those with viral infection, 68 patients were identified and categorized as an autoimmune hepatitis. Age of the patients, sex and Khat chewing habit were recorded. Alcohol consumption habit if any was also noted. Viral markers were tested for hepatitis A, B and C. All of the patients underwent serum bilirubin, liver function tests (AST and ALT); and also albumin and G-globulin. Auto-antibodies- antinuclear antibodies (ANA), anti-smooth muscle antibodies (SMA), antibodies to liver/kidney microsome type 1 (LKM-1) and anti-mitochondrial antibodies (AMA) were also tested. Ultrasonography of the abdomen was also performed to all patients. All patients received the same treatment using the following conventional regimen; Prednisolone 30 mg / 24 hours and Azathioprine 100 mg / 24 hours. Those patients, who are taking drugs that has been

implicated in the etiology of autoimmune hepatitis has been excluded. The commonly used of these drugs include: Statins, Ezetimib, Nitrofurantoin, Risperidone, Ranitidine, non-steroidal anti-inflammatory agents and some of the anti-tuberculosis agents as: Rifampicin and Pyrazinamide.

RESULTS

There were 68 patients in this study with a mean age of 28.3 years (range: 15 - 60). Seventy five percent of the patients were males (4:1 male to female ratio). This is in contrary to published data of (1:4 of male to female ratio). Eighty five percent of the patients were Khat chewers. The age distribution showed typical bimodal distribution of type 1 AIH (Figure -1). Liver function tests: ALT and AST were elevated in all patients but 47% of which showed marked rise (Figure -2). All patients showed hyperbilirubinemia between 8-35 mg/dl. Albumin was low in 54.5% of the patients indicating severe liver injury with impaired synthetic functions, and G-globulin was elevated in 72% of the patients. In 47% of the patients there were more than threefold increase in both AST and ALT and even in about a quarter of them exceeded ten folds. Antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) were positive in 76.8% and 61.8% of patients, respectively (Figure -3). Furthermore, antibodies to liver/kidney microsome type1(LKM-1) was positive in one patient only, and this may indicate that is related to type 2 AIH. Liver imaging did not reveal obstructive pathology. In addition to Khat chewing abstinence, all patients underwent similar conventional regimen of therapy and about 80% showed a positive response to this treatment while the rest of them responded to either higher doses or alternative therapeutic regimens. Six percent of the patients showed an association with other forms of autoimmune diseases.

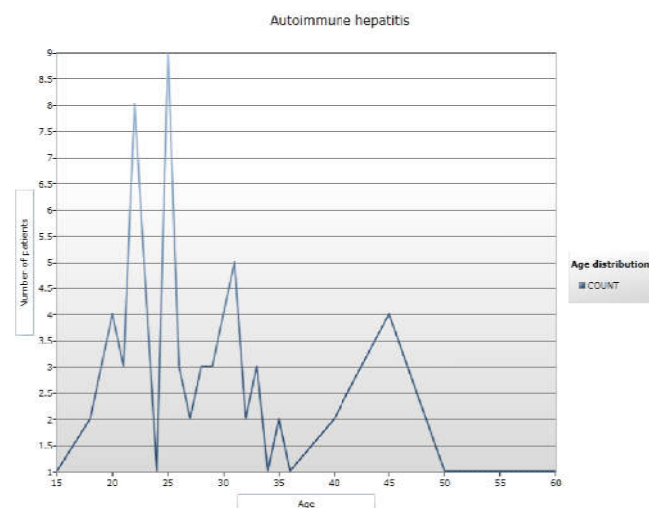


Figure 1. Age distribution

DISCUSSION

The pathogenesis of AIH postulates that environmental factors might trigger its appearance, a failure of immune tolerance mechanisms, and a genetic predisposition collaborate to induce a T cell-mediated immune attack upon liver antigens, leading to a progressive necro-inflammatory and fibrotic process in the liver. Biggazzie; have demonstrated in the immunotoxicological studies, that autoimmune responses and / or autoimmune diseases are induced in humans and

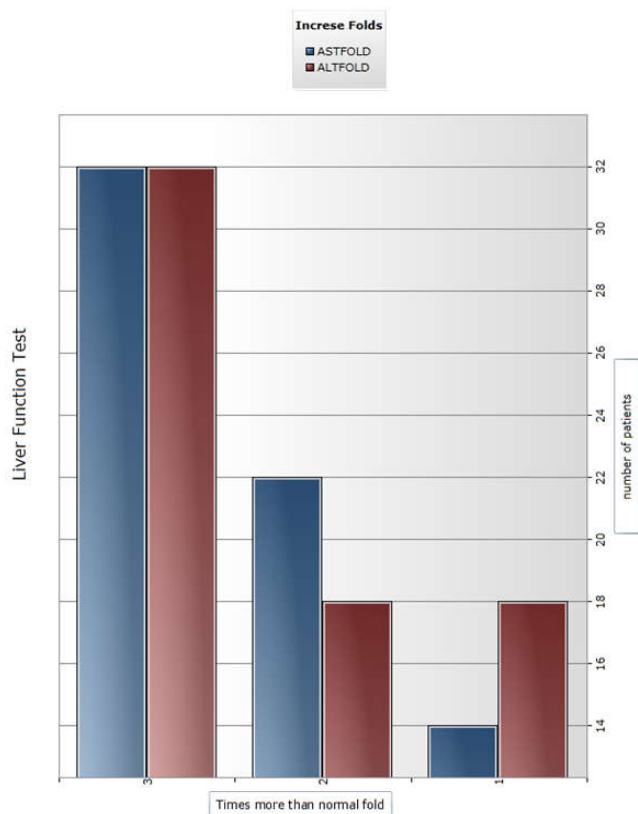


Figure 2. AST & ALT folds

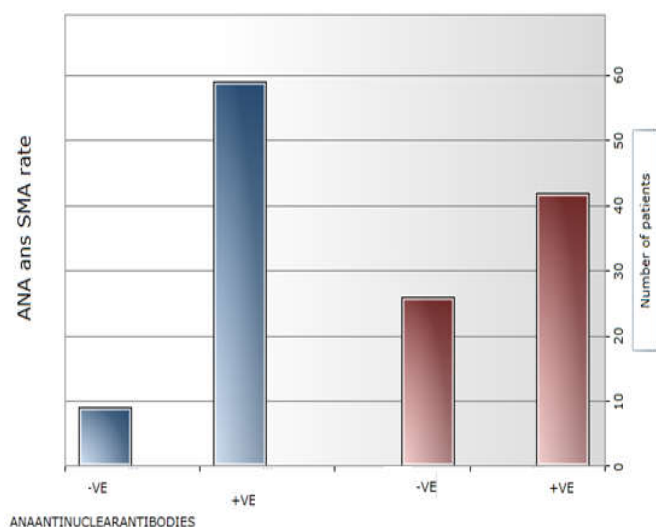


Figure 3. Autoantibodies (ANA & SMA)

experimental animals by chronic exposure to various chemicals. Recently, there is some concern about the role of pesticides and its immune-toxic risk. Overall, the available data are inadequate to draw firm conclusions of that (Alvarez, 1999). The diagnostic criteria for AIH and a diagnostic scoring system were codified by an international panel in 1993 (Corsini, 2008), and revised in 1999 (Roelandt, 2011). Although a relatively recent revised classification of AIH includes forms associated with viral C, but our clinical criteria for the diagnosis of our cases depended on the seropositivity for ANA, anti-SMA or anti-LKM-1 antibodies, and seronegativity for markers of current infection with hepatitis A, B and C viruses. These with the clinical picture and negative alcohol consumption and excluding medication that

are known to cause hepatitis were sufficient to make or exclude definite or probable AIH in the majority of patients. It is well known in Yemen that males consume Khat more than females, which explains the higher rate of males presented with AIH in the present study. We believe that this is the first study performed on a wider scale that shows a direct relation between this cursed plant and its insult on the liver tissue and the aim of the study was to establish the relation between Khat chewing habit and acute autoimmune hepatitis. Riyaz S *et al*, (Riyaz, 2014), recently reported six patients from the UK who presented with acute hepatitis on a background of Khat. All were males and five of these patients were of Somali origin, while one patient was from Yemen. All these patients were treated with prednisolone and demonstrated a good response to immunosuppression. Roelandt *et al*, reported a 26 years old male patient developed acute liver failure secondary to ingestion of Khat (*Catha Edulis*) leaves. Clinically, the presentation was autoimmune-like hepatitis (de Boer, 2017). The effect of Khat might persists after drug discontinuation, suggesting that they awaken latent autoimmunity. At least three clinical scenarios have been proposed that refers to drug-induced autoimmune liver injury:

Clinical and serologic features of drug-induced AIH resemble that of the idiopathic one (de Boer, 2017), and our patients typically demonstrated an obvious similarity with a picture of drug induced liver injury with autoimmune features accompanied by development of auto-antibodies. Predictable toxicities and idiosyncrasies account for a high proportion of hepatotoxic effects while, for the remainder, the immune system is an essential culprit. Toxin-induced immune injury to hepatocytes would depend on conjugation of a reactive metabolite which may generate cell damage directly or by creation of neo-antigen. The consequent response is expressed as hepatocellular damage and production of auto-antibodies that simulate that spontaneous AIH. The pathogenesis of these events in general is still opaque since genetic polymorphisms can influence the immunologic reactivity (Makay, 1996). Moreover, collateral factors such as intrahepatic inflammatory stress can potentiate the hepatic reactivity to the different insults (Andrade, 2004).

Aminotransferase elevations with serum autoantibodies are usually present, including antinuclear (ANA), anti-smooth muscle antibody (SMA) and to a lesser degree to liver-kidney microsome-1 (LKM-1) (de Boer, 2017). Immunoglobulin levels and total globulins are often but not always raised (Watkins, 2006). AIH is not clear whether it is triggered rather than caused by the Khat and this will need additional studies. Therefore, tasks for the future include the better understanding the pathogenesis of AIH, ideally through the development on animal models faithfully reproducing the human disease and the establishment of novel treatments. Owing to the recent concern about the hazards related to the pesticides used in the this plant cultivation, it is quite clear from laboratory and results of various studies that unregulated use of pesticides of all categories may influence immune system in humans resulting in its dysfunction. But unfortunately, the available data are inadequate to draw firm conclusions on the immune-toxic risk associated pesticide exposure (Bigazzi, 1998 and Street, 1981).

CONCLUSION

Khat-related AIH has clinical and serologic features resembling that of the idiopathic one. AIH in Yemen is not

clear whether it is triggered rather than caused by the Khat and the above needed researches are advised. Studies are preferably to be prospective, comprising pre- and post-pesticides' exposure data in the same group of subjects and including an appropriate non-exposed control group. This may also prove or exclude the immuno-toxic role of the active ingredient (cathinone) of the Khat's leaf. In Yemen, Khat chewing constitutes a big socio-economic and health burden rendering some journalists and scientists to call our country's liver's burden as: "the plague of Yemen", "Yemeni sheep's liver" and "Yemeni liver's curse". Therefore, the related governmental and non-governmental institutions must increase the awareness and education regarding the different hazards at least to limit its cultivation or even to consider prohibiting of Khat consumption, like the recently issued official similar rule in the UK and Malaysia.

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