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Clinical Features and Laboratory Findings in Mad Honey Intoxication: A Retrospective Study

Ozcan Piskin[1], Derya Arslan Yurtlu[2], Bengu Gulhan Aydin[1], Yusuf Cemil Gursoy[3], Volkan Hanci[4]

ABSTRACT:

Clinical features and laboratory findings in mad honey intoxication: a retrospective study

Objective: Mad honey intoxication results from consuming honey which is produced from rhododendron flowers and containing Grayanotoxin (GTX). This intoxication is seen rarely, however it may lead some life-threatening signs. In this study, it was aimed to retrospectively discuss the effects of 38 mad honey intoxication cases on the organs in the light of demographic and biochemical blood gas parameters.

Material and Methods: We enrolled 38 patients diagnosed with "mad honey intoxication" retrospectively, who were admitted to our emergency department between January 2010 to December 2012.

Results: Of cases, 23 (60.5%) were male and 15 (39.5%) were female. Our cases were between the ages of 29 and 86 years. The mean age of cases was 55.42±12.63 years. The mean onset of symptoms after honey intake was determined to be 92.82±30.09 minutes. The mean heart rate when cases applied to hospital was found to be 49.74±11.41 beats/min. and the mean systolic and diastolic blood pressures were found to be 72.16±16.92 mmHg and 43.79±10.58 mmHg, respectively. The mean amount of atropine treatment given to the patient was found to be 0.76±0.55 mg and the mean crystalloid fluid given was 1336.84±935.31 mL. Except the rhythm problems, gastrointestinal, respiratory and cardiovascular system findings were in normal range. There was no correlation found between the amount of honey consumed and the onset of symptoms in the cases.

Conclusion: Mad honey intoxication most often affects the cardiovascular system. Hypotension and bradycardia are the most common signs in these patients. Sufficient fluid hydration and 1-2 mg intravenous atropine are often adequate for the treatment.

Keywords: Intoxication, grayanotoxin, GTX, mad honey

ÖZET:

Deli bal zehirlenmesinde klinik özellikler ve laboratuar bulguları: Retrospektif bir çalışma

Amaç: Deli bal zehirlenmesi; Rhododendron çiçeklerinden üretilen ve içinde Grayanotoxin (GTX) bulunan balın tüketilmesi sonucunda oluşur. Oldukça nadir görülmesine ragmen hayatı tehdit eden bulgulara sebep olabilir. Bu çalışmada hastanemize başvuran 38 deli bal zehirlenmesi vakasının demografik ve biyokimyasal kan gazı paremetreleri ışığında organlar üzerindeki etkilerinin retrospektif olarak literatür eşliğinde tartışılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya 2010-2012 yılları arasında acil servise herhangi bir şikayetle başvurmuş ve 'Deli Bal Zehirlenmesi' tanısı almış toplam 38 hastanın retrospektif dataları dahil edildi.

Bulgular: Olguların 23 (%60.5)'i erkek, 15 (%39.5)'i bayandı. Olgularımız 29 ile 86 yaşları arasındaydı. Olgularımızın yaş ortalamaları 55.42±12.63 yıl olarak belirlendi. Olguların bal alımı sonrası semptomların başlama süresi ortalama 92.82±30.09 dak olarak belirlendi. Olgularda hastaneye başvurudaki kalp atım hız ortalaması 49.74±11.41 atım/dak, ortalama sistolik kan basıncı değeri 72.16±16.92 mmHg ve ortalama diyastolik kan basıncı 43.79±10.58 mmHg olarak bulundu. Hastaların ortalama 0.76±0.55 mg atropin ve 1336.84±935.31 ml kristaloid sıvı ile tedavi edildiği bulundu. Ritm problemleri dışında gastrointestinal, solunum ve kardiyovasküler sistem bulguları normal sınırlardaydı. Olguların bal tüketim miktarları ile, semptomların başlama süresi arasında bir korelasyon ilişkisi belirlenemedi

Sonuç: Deli Bal Zehirlenmesi en sık kardiyovasküler sistemi etkilemektedir. Bu hastalarda en sık hipotansiyon ve bradikardiye rastlanmaktadır. Tedavide sıklıkla yeterli sıvı resüsitasyonu ve 1-2 mg İntravenöz Atropin tedavisi yeterli olmaktadır.

Anahtar kelimeler: Zehirlenme, grayanotoksin, GTX, deli bal

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[1]Bulent Ecevit University, Department of Anesthesia and Reanimation, Zonguldak - Turkey
[2]Katip Çelebi University, Department of Anesthesiology and Reanimation, Izmir - Turkey
[3]Bulent Ecevit University, Department of Anesthesia and Reanimation, Zonguldak - Turkey
[4]Bulent Ecevit University, Department of Cardiology, Zonguldak - Turkey
[5]Dokuz Eylul University, Department of Anesthesia and Reanimation, Izmir - Turkey

Address reprint requests to / Yazışma Adresi:
Ozcan Piskin,
Bulent Ecevit University, Department of Anesthesia and Reanimation, Zonguldak - Turkey

E-mail / E-posta:
drozcanp@gmail.com

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INTRODUCTION

Mad Honey intoxication is caused as a result of consuming honey which is produced from Grayanotoxin (GTX) containing rhododendron flowers (1,2). The rhododendron plant is mainly found in the western Black Sea region of Turkey and also in Nepal, and the north and western regions of the American continent (2). Grayanotoxin is produced in the pollen and nectar parts of the rhododendron plant. In Turkey, R. Luteum and R. Ponticum, are the common species that cause poisoning (3). Though many GTX types have been identified, types GTX-I and III primarily have toxic content (4).

During intoxication cases of hypotension and deep bradycardia mainly occur, with cardiovascular findings at the forefront from nodal rhythm even progressing to asystole (5-7). Gastrointestinal and central nervous system findings are itching in the mouth and nose, reddening of eyes and skin, headache, vertigo, nausea, vomiting, salivation, cramp-like stomach pain, urinary and fecal incontinence, gastroenteritis, weakness, blurred vision or temporary blindness and delirium, possibly coma (1,2,5,8,9). Rare case reports have reported that mad honey intoxication may cause hepatotoxicity (10).

Mad honey is consumed as an alternative medication for the treatment of stomach pain, intestinal disorders, hypertension and sexual dysfunction in Turkey, especially in the Black Sea region (11). Thus, poisoning cases are frequently encountered in this region. Though a literature review reveals publications of case reports or case series, we did not find any study regarding the changes in biochemical parameters of mad honey intoxication cases.

This study aimed to retrospectively examine the effects of mad honey intoxication on organs of 38 cases who admitted to our hospital between 2010 and 2012 in the light of demographic and biochemical blood gas parameters, and discuss in relation to the literature.

MATERIALS AND METHOD

The study was conducted at an urban state hospital with more than 200.000 emergency department visits yearly. After receiving informed patient consent, we described and retrospectively enrolled 38 cases with the diagnosis of "Mad Honey Intoxication" admitted to our emergency department between January 2010 to December 2012 in Zonguldak, a city on the coast of the Black Sea. Mad Honey intoxication was diagnosed by history of consumption of locally prepared, non-processed honey and findings of dizziness, nausea, ataxia, bradyarrhythmia, diaphoresis and hypotension, which are the typical signs of mad honey intoxication.

In addition to the demographic information such as age and gender of patients, information about the mad honey intoxication such as the duration between intake of honey and onset of symptoms, blood pressure values and heart rate at the time of hospital administration, rhythm analysis results, laboratory data [Glucose, Blood urea nitrogen (BUN), Creatinine, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), Alkaline phosphatase, Lactate dehydrogenase (LDH), Creatine kinase (CK), Creatine kinase-MB (CK-MB), Amylase, Lipase, Sodium (Na), Potassium (K), Chloride (Cl) , Calcium (Ca), Total bilirubin (T-Bil), Direct bilirubin (D-Bil), White blood cell (WBC), Hemoglobin (Hg), Hematocrit (Hct), Platelet (Plt), pH, pO_2, pCO_2, HCO_3, sPO_2, Lactate, Myoglobin, Troponin-I (Tro-I)], monitoring period in the emergency service, treatment given in emergency service, intensive care treatment and whether temporary pace-maker was used, were all determined and recorded.

The study was approved by Zonguldak Bulent Ecevit University Faculty of Medicine ethical committee on 12 June 2012 (no:2012-70-02/05).

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) 15.0 program. Continuous variables such as patient age, duration of hospital stay, heart rate, systolic and diastolic blood pressures are shown as mean ± SD. Frequency data such as gender distribution are given as number and percentage. Distribution analysis of data was completed with the Kolmogorov-Smirnov test. Comparisons between the groups were made

with the Mann-Whitney U test and the chi-square test and a value of $p<0.05$ was accepted as a significant difference.

RESULTS

A retrospective analysis from January 2010 to December 2012 was conducted with 38 patients with a diagnosis of mad honey intoxication, diagnosed at the emergency service unit of Zonguldak Atatürk State Hospital.

Table-1: Demographic, clinical characteristics and treatment of patients with mad honey intoxication

	n (%), mean±SD
Meanage, years	55.42±12.63
Gender (F/M)	15/23
Amount of honeyingested, spoonful	1.63±1.05
Time fromingestiontoonset of symptoms, min	92.83±30.09
Systolicbloodpressure, mmHg	72.16±16.92
Diastolicbloodpressure, mmHg	43.79±10.58
Pulse rate, beat.min^{-1}	49.79±11.41
Dosage of Atropine, mg	0.760±0.55
Saline, mL	1336.84±935.31
ECG Rhythms, %	
Sinusbradycardia	31 (81.5)
Normal sinüs rhythm	4 (10.6)
Nodal rhythm	1 (2.6)
Complete AV block	1 (2.6)
Slow ventricular response atrial fibillation	1 (2.6)

SD: standard deviation, AV: Atrioventricular

Of cases, 23 (60.5%) were male and 15 (39.5%) were female. Our cases were between 29 and 86 years old. The average age of cases was 55.42±12.63 years. The average age of male cases was 53.48±12.83 years, while for female cases this was 58.40±12.13 years. There was no significant difference between the average ages according to gender ($p>0.05$) (Table- 1).

The duration between consumption of honey and onset of symptoms varied between 45 and 1800 minutes, with the average onset of symptoms after honey consumption determined to be 92.82±30.09 minutes. While the duration until the onset of symptoms was determined as 88.78±26.24 minutes for males, this duration was 99.00±35.25 minutes for female cases. There was no significant difference between the duration until the onset of symptoms by gender ($p>0.05$).

When the amount of honey consumed by patients was analyzed, 25 patients (65.8%) had 1 table spoon, 6 (15.8%) had 2 table spoons, 4 (10.5%) had 3 table spoons, 2 (5.3%) had 4 table spoons while 1 patient (2.6%) showed intoxication signs after consuming 5 table spoons of honey. The average consumption of honey was determined as 1.63±1.05 table spoons. In male cases the average honey consumption was 1.60±1.12 table spoons while it was 1.65±1.027 table spoons for females. There was no significant difference between the average consumption of honey by gender ($p>0.05$). There was no correlative

Table-2: Hematologicalparemeters of patientswith mad honeyintoxication

	mean±SD	Normal range
WBC, K.uL^{-1}	6.963±2.039	4.800-10.800
Hemoglobin, g.dL^{-1}	13.2±1.41	12-18
Hematocrit, %	38.81±3.42	37-52
Platelets, K.uL^{-1}	200.470±52.017	140.000-400.000

SD: standard deviation, WBC: White bloodcell

Table-3: Blood gasparemeters of patientswith mad honeyintoxication

	mean±SD	Normal range
pH,	7.36±0.31	7.35-7.45
pO_2, mmHg	91.93±20.09	80-100
pCO_2, mmHg	48.37±16.32	35-45
HCO_3, mEq.L^{-1}	25.33±2.27	95-99
Lactate, mEq.L^{-1}	1.88±0.97	0.7-2.1

SD: standard deviation

Table-4: Biochemical paremeters and cardiac markers of patients with mad honey in toxication

	mean±SD	Normal range
Glucose, mg.dL^{-1}	111.87±38.31	70-115
Urea, mg.dL^{-1}	36.71±12.13	0-50
Creatinine, mg.dL^{-1}	0.993±0.2392	0-1.40
AST, u.L^{-1}	25.08±17.75	0-35
ALT, u.L^{-1}	24.97±20.63	0-50
GGT, u.L^{-1}	27.00±18.38	0-32
T-Bil, mg.dL^{-1}	0.515±0.303	0-1.1
D-Bil, mg.dL^{-1}	0.215±0.936	0-0.4
ALP, u.L^{-1}	78.82±28.68	43-170
LDH, u.L^{-1}	172.433±39.036	0-247
CK, u.L^{-1}	103.92±71.696	50-150
CK-MB, u.L^{-1}	12.87±11.667	0-4.94
Troponin I, mg/dL	0.0072±0.1104	0-0.03
Myoglobin, mg.dL^{-1}	73.24±34.866	10-90
Amylase, u.dL^{-1}	60.32±26.23	28-100
Lipase, u.L^{-1}	34.18±23.80	0-60
Sodium, mEq.L^{-1}	139.54±2.12	132-146
Potassium, mEq.L^{-1}	4.19±0.56	3.5-5.5
Chloride, mEq.L-1	106.37±2.73	96-110
Calcium, mg.dL^{-1}	9.013±0.511	8.8-10.6

SD: standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, T-Bil: Bilirubin-Total, D-Bil: Bilirubin-Direct, ALP: Alkaline Phosphatase, LDH: Lactic Dehydrogenase, CK: Total CreatinineKinase, CK-MB: Creatinine Kinase-MB

relationship found between the amount of honey consumed by cases and the duration until the onset of symptoms (p=0.981).

Heart rates at the time of arrival to the hospital varied between 26 and 118 beats per minute, with an average value of 49.74±11.41 beats/min. When cases admitted to hospital, systolic blood pressure value varied from 50 mmHg to 110 mmHg, with an average of 72.16±16.92 mmHg. The diastolic blood pressure values varied from 25 mmHg to 60 mmHg, with an average of 43.79±10.58 mmHg (Table-1).

There was no significant relationship or correlation found between gender, amount of honey consumed and duration until the onset of symptoms, and heart rate, systolic blood pressure and diastolic blood pressure (p>0.05).

When the ECG analyses of cases were evaluated, 1 case (2.6%) had complete atrioventricular block, 1 (2.6%) had low ventricular response atrial fibrillation, 1 (2.6%) had nodal rhythm, 4 cases (10.6%) had normal sinus rhythm and 31 cases (81.5%) had sinus bradycardia (Table-1).

When the laboratory data of cases were evaluated, there was no significant correlation between increased consumption of honey and laboratory analyses (p>0.05).

The correlation analyses between the time of onset of symptoms and laboratory analyses showed an increase in amylase (r=0.373; p=0.021) lipase (r=0.407; p=0.011) levels and a reduction in calcium levels (r=-0.461; p=0.004) with prolonged time of onset of symptoms (p<0.05). There was no significant correlation found between other laboratory analyses and duration to onset of symptoms (p>0.05) (Table-2), (Table-3), (Table-4).

In the light of these findings, cases who were given treatment of atropine varying from 0.5 to 3.5 mg with an average of 0.76±0.55 mg and between 500 to 3500 mL crystalloid fluid with an average of 1336.84±935.31 mL discharged from the emergency service unit.

Among our cases there was no patient with morbidity or mortality related to mad honey intoxication.

DISCUSSION

Mad honey, believed to be an alternative treatment for diseases such as gastritis, intestinal problems, hypertension and diabetes mellitus and to increase sexual performance, has been frequently consumed throughout history in the Black Sea region of Turkey

and is a topic of many folk legends (3,11,12).

Mad honey intoxication develops as a result of consuming honey produced from rhododendron flowers that contain GTX (1,2). GTX binds to voltage-dependent sodium channels selectively causing hyperpolarization. This situation causes changes such as activation or inactivation of cell membranes (13). Symptoms occur due to these changes in the membranes of the cells of the skeletal system, cardiovascular system and central nervous system (11).

In case series, it is seen that mad honey intoxication frequently affects the middle-advanced age group and the male gender (1,8,14,15). Hancı et al. (1) in a study investigated 72 cases and reported that 81.9% of the cases were male. The same study reported the ages ranged from 23-78 years and the average age was 49.46±11.11. Gündüz et al. (8) in a study of 48 cases, reported 85% were male and the average age was 56.3±12.2. In a study of 46 cases by Uzun et al. (14), 36 of the cases were male and the average age was reported as 52.2±17.2 years. Similarly in our study 60.5% of cases were male; their ages ranged from 29 to 86 with an average of 55.42±12.63 years. People believe that mad honey is a beneficial alternative treatment for diseases such as hypertension and diabetes mellitus and increases sexual performance and we consider this is why cases are more frequently seen in the middle-advanced age group and in the male gender.

It has been observed that clinical signs of mad honey intoxication are directly correlated with the amount of honey consumed and begin a short time after consumption (1,5,8,14,15). Hancı et al. (1) in a study found the amount of honey consumed to cause intoxication varied from 15 to 60 grams and symptoms began an average of 78.54±37.46 minutes after consumption of honey. Yılmaz et al. (15) in their study reported that the amount of honey causing intoxication was 13.45±5.39 (5-30) grams and symptoms began 1.19±0.65 (0.5-3) hours after consumption. Similarly in our study cases had consumed an average of 1.63±1.05 table spoons of honey before intoxication and symptoms began an average of 92.83±30.09 minutes after consumption.

The majority of mad honey intoxication cases apply to hospital with complaints of bradycardia and hypotension (1,8,15,16). Gündüz et al. (8) in their study found the average heart rate at time of application to hospital was 46.6±12.1 beats.min^{-1}, average systolic blood pressure was 79.86±19.04 mmHg and average diastolic blood pressure was 51.6±15.5 mmHg. Cases reported by Yılmaz et al. (15) had an average heart rate of 47.96±8.48 beats.min-1, average systolic blood pressure of 70.08±14.89 mmHg and average diastolic blood pressure of 45.25±12.91 mmHg at time of application to hospital. In our study when our cases applied to hospital the average heart rate was 49.79±11.41 beats.min^{-1}, average systolic blood pressure was 72.16±16.92 mmHg and diastolic blood pressure of 43.79±10.58 mmHg. These findings were comparable to those of previous cases series.

Mad honey intoxication most often affects the cardiovascular system (1,2,5-9,15-19). Most of the case series in the literature report varying degrees of cardiac rhythm problems. In a study evaluating 47 patients by Gündüz et al. (8), it was reported that the most frequently observed was sinus bradycardia (78.7%), followed by nodal rhythm (12.8%), normal sinus rhythm (6.4%) and complete AV block (2.1%). In our study the most frequently observed was sinus bradycardia (81.5%), followed by normal sinus rhythm (10.6%), nodal rhythm (2.6%), complete AV block (2.6%) and slow ventricular response atrial fibrillation (2.6%). In the literature in addition to rhythm disorders, there are rare cases of myocardial infarctus linked to bradycardia and deep hypotension (20,21). In a case reported by Yildirim et al. (20), a 41-year old male patient applied to the emergency service 3 hours after consuming mad honey with severe chest pain. The patient's troponin-I value was 0.4 mg.dL^{-1} and creatinine kinase MB value was 18.1 u.L^{-1}. After ECG and other laboratory investigations, the patient was diagnosed with non-ST-segment elevation myocardial infarction and treatment was given. In our cases no patient had diagnosis of myocardial infarct. The average cardiac enzymes (Tro-I, CK, CK-MB, Myoglobin) of our cases were within normal limits.

Onat et al. (22) in an animal experiment using rats, investigated the effects of GTX on the cardiovascular, pulmonary and central nervous system. At the end of the study they showed that GTX induced bradycardia

and respiratory depression. However in our study no patient had respiratory depression. The average blood gas sample results of our cases were as follows: pH: 7.36±0.31, pO_2: 91.93±20.09 mmHg, pCO_2: 48.37±16.32 mmHg, HCO_3: 25.33±2.27 mEq.L^{-1} and Lactate: 1.88±0.97 mEq.L-1. Our literature review showed no isolated respiratory depression linked to mad honey intoxication. We consider that this result may be related to the low average amount of honey consumed.

Öztaşan et al. (23) investigated the effects of GTX on blood sugar. After inducing experimental diabetes with Streptozotocin in rats, GTX was administered to the diabetic rats and blood lipid and glucose levels were shown to fall. In a prospective study investigating the effects of mad honey intoxication on blood sugar by Uzun et al. (14), they reported no statistically significant fall in blood sugar levels linked to mad honey intoxication. Similarly in our study average blood glucose was 111.87±38.31 mg.dL^{-1}. We observed that symptoms began an average of 92.83±30.09 minutes after honey consumption in our study. This duration is within the limits of postprandial blood sugar levels. Due to the retrospective planning of our study, blood glucose levels prior to consumption of mad honey were not known, and there was no case with isolated diabetes. Thus, no conclusion can be drawn about blood glucose changes following GTX exposure.

Aşçıoğlu et al. (24) investigated the effects of GTX on the hepato-renal system. Rats given high dose of GTX-I developed proteinuria and hematuria, however they reported no changes in histopathology. The same study showed that the liver was affected more. Rats given GTX-I had widening of the hepatic central vein, congestion of the hepatic parenchyma, focal necrosis and inflammatory changes together with biochemical increase in transaminases. Çetin et al. (10) reported a case with a history of consuming honey who developed hepatotoxicity. The case with progressive increase in transaminases fully recovered after medical treatment and was discharged. In our cases, no patient had signs of hepatotoxicity and nephrotoxicity. But the correlations between the time of onset of symptoms and laboratory analyses showed an increase in the amylase and lipase levels and a reduction in the calcium levels with increased time of onset of symptoms. In a study evaluating 4340 patients, Steinberg W.M. et al. (25) reported that nearly 25% had elevated lipase or amylase levels without symptoms of acute pancreatitis. GTX can affect both sodium and calcium canal receptors. Kim S.E et al. (26) investigated the effects of GTX III on synaptic transmission in VMH neurons. They indicated that GTX increases Ca^{2+} influx through voltage-dependent Ca^{2+} channels secondary to activation of voltage-dependent Na^{+} channels in inhibitory and excitatory nerve terminals synapsing on neurons. Ca^{2+} may also enter presynaptic terminals via reduced Ca^{2+} extrusion from the forward transport mode of the Na^{+} /Ca^{2+} exchanger (26). We think that our results may be due to the interaction between sodium and calcium at the receptor level.

The treatment of mad honey intoxication includes sufficient fluid hydration and 1-2 mg intravenous (IV) atropine for the symptoms to regress and rarely a pacemaker may be required (1,2,8,14-19,27). Hancı et al. (1) found that after treatment with an average of 0.59±0.36 mg atropine and 746.58±242.90 mL saline, 98.6% of cases had normal sinus rhythm and normal blood pressure values. In our study after infusion of 0.760±0.55 mg IV atropine and 1336.84±935.31 mL saline, cases were observed to have normal sinus rhythm and normal blood pressure values. Additionally, none of our cases required a pacemaker.

While it is observed that many mad honey intoxication cases return to normal vital signs after 24 hours of IV atropine and fluid hydration treatment, the variety of clinical applications in the follow-up period seen in literature are interesting (8). Özhan et al. (28) reported that they observed their mad honey intoxication cases for 24 hours in their clinic and then discharged. In another study, the patients with slight intoxication were discharged after 2-6 hours of cardiac monitoring, while the significant symptoms and findings disappeared with no treatment within 24 hours (8,11).

An important limitation of this study is its retrospective design. During the retrospective investigation of our records, we found contradictory information about the duration of hospital stay for cases; as a result we had to exclude the duration of

hospital stay from the discussion. Additionally, during the scan of the records we found that the number of mad honey intoxication cases applying to the emergency service was higher than thought; however as a result of inadequate anamnesis they were monitored with prediagnosis of iatrogenic bradycardia or iatrogenic hypotension. We had to exclude these patients from the study.

Though mad honey intoxication is frequently observed in the Black Sea region, there is no standard algorithm and guidelines for diagnosis and treatment of these cases. As a result, there may be differences in diagnosis and treatment protocols between clinics. This situation may cause negative results for mad honey intoxication due to diagnosis and treatment.

CONCLUSION

The majority of mad honey intoxication cases are seen in the male gender and cases most frequently apply to health centers with bradycardia and hypotension symptoms. Regression of symptoms occurs after 1-2 mg IV atropine and sufficient fluid hydration. In the future to fully determine the effects of GTX on all organ systems, stronger studies with more subjects are needed.

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