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Original Research

Clinical Presentation, Electrocardiographic Findings, and Factors Related to the Hospitalization In Mad-Honey Intoxication

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Abstract

Objectives: Mad-honey intoxication (MHI) often presents with all kinds of bradyarrhythmias. Despite numerous publications focused on clinical findings, we aim to evaluate poor prognostic implications, ischemia likely electrocardiography (ECG) changes, and detailed ECG findings of MHI in the largest series.

Methods: This is a retrospective single-center study of 117 MHI patients admitted to emergency service.

Results: The study had 26 (22.2%) females (median 52.5 years) and 91 (77.8%) males (median 51.0 years). Fifty-six (47.9%) patients had ischemia likely changes on ECG. Multivariate model demonstrated that beta-blocker usage (odds ratio (OR): 52.871; 95% confidence interval (CI): 3.618-772.554 (p=0.004)), atrioventricular junctional rhythm (AVJR) (OR: 5.319; 95%CI: 1.090-25.949 (p=0.039)), and quantity of mad-honey consumption (OR: 1.035; 95% CI: 1.008-1.063 (p=0.011)) are predictors of hospitalization. ROC curve analysis showed cutoff value of mad-honey consumption quantity 24.79 g had 57% sensitivity and 68% specificity for predicting hospitalization (AUC: 0.7, 95% CI: 0.55-0.816, p=0.027). In addition, all hospitalized cases were male.

Conclusion: Our study has shown that male gender, AVJR, the quantity of mad-honey consumption, and beta-blocker usage are high-risk criteria for hospitalization in MHI patients. Furthermore, ischemia likely ECG changes is often observed with MHI even independently from hypotension or bradycardia.

Keywords: Bradycardia, cardiac arrhythmias, cardiotoxicity, food poisoning, honey, plant poisoning

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Grayanotoxin is found on leaves, nectar, and pollen of Rhododendron species.[1] Mad-honey intoxication (MHI) frequency in society varies according to distribution of grayanotoxin including flowers abundance in natural flora. Rhododendron species are frequently present in mountains in the Black Sea region. Moreover, grayanotoxin transmission to honey frequently happens which is produced by honeybees from nectars of Rhododendron genus. After ingestion of honey that is made from these plants' pollen, a cholinergic toxic syndrome picture emerges, which is called MHI.[2] Mad-honey affects every organ of body, but most dramatic evidence of its disruptive behavior appears on the heart. Grayanotoxin binds with the sodium channel, moves the membrane potential in a hyperpolarization direction, and behaves like a cholinergic agent.[3,4] As a result of this, grayanotoxin has negative chronotropic and dromotropic effects.[5] Moreover, MHI demonstrates a wide spectrum of clinical findings: Bradyarrhythmias, hypotension, and respiratory depression.[6,7]

Numerous publications show bradydysrhythmias, additionally, to be known in our report; we aim to interpret electrocardiography (ECG) findings in detail even according to atrioventricular dissociation (AVD) and atrioventricular junctional rhythm (AVJR) types.

Depending on severity of hypotension or arrhythmia, these patients may become symptomatic. Among severe bradyarrhythmias, usually proceed clinically benign.[2,8] However, MHI can cause life-threatening statements such as asystole.[9] or very rarely fatality.[10] To assess the clinical significance of MHI, adverse events (hospitalization, long emergency service follow-up time, and poor vital signs) are the best modalities and crucial in terms of guiding the treatment to be applied. Nevertheless, in the literature, researches about predictors of adverse events in MHI remain unknown. Hence, we design our study to determine poor prognostic clinical implications of MHI.

Clinical trials about cardiac ischemia effects of MHI in the literature are very rarely even as case reports (acute myocardial infarction and non-ST elevation myocardial infarction).[11-15] Moreover, in a review, ST-segment elevation was observed with a ratio of 22.63%.[2] Based on this observation, we planned to evaluate ischemia likely ECG changes in MHI.

Mad-honey has frequently been consumed especially for traditional medicine. Even, some patients have been consuming mad-honey for a long time. However, only one report presents data about chronic toxicity effects of mad-honey.[16] In our study, some cases have a history of regular daily intake of mad-honey. In this manuscript, we report data regarding our experience in chronic MHI outcomes.

Despite many reports in the literature, our study is unique in the field, as it provides an opportunity to explore new demographic events, comprehensive ECG findings, ischemia likely ECG events, and poor clinical implications in largest MHI cases. This study may help colleagues better evaluate patients, improve monitoring of vital signs, and also benefit the future development of MHI risk stratification algorithms.

Methods

Study Design and Population

A single-center cohort study was performed to evaluate patients for clinical, electrocardiographic outcomes, and poor prognostic factors of MHI.

We have retrospectively reviewed the medical records of 246 patients admitted to emergency service with a diagnosis of MHI. MHI diagnosis was performed from the history of the suspicious honey consumption and clinical manifestations. Patients were included in the study if MHI definition criteria were applicable and no doubt existed about the diagnosis. All confirmators, reviewers, and abstractors were blinded to the study. Eventually, all possible cases of MHI that were included on basis of the algorithm were confirmed by an expert (at least post-fellowship experience of 5 years). One hundred and twenty-nine patients were excluded due to insufficiency of medical records. One hundred and seventeen patients were included in the study. Demographic findings of patients and laboratory values were recorded. All clinical, electrocardiographic data were retrospectively collected from the archive of the Social Insurance Institution Database for 1-year period of history. The hospital's information management system records, emergency room patient follow-up forms and medical charts, notification forms of poisoning (Form 018/C) cases' findings, medical files, clinical laboratory findings, and hospital discharge records consist of information on diagnosing, the reason for admission and discharge, vital signs (heart rate, blood pressure), and secondary findings are evaluated.

Electrocardiographic Analysis

The 12-lead ECG was performed before admission of atropine or any other medication. ECG was evaluated by the two double-blinded consultant cardiologists (at least post-fellowship experience of 5 years) for arrhythmias and presence, absence of ischemia likely ECG findings (ST-segment elevation and/or depression, T wave inversion, Q wave, biphasic, or flattened T wave).

Patients with AVD rhythm were divided into two groups with a 3rd-degree atrioventricular block (AVB) and without. Then, subgroups without 3rd-degree-AVB were evaluated for accrochage or isorhythmic types. Furthermore, AVJR

patients were divided into subgroups according to heart rates and defined as AVJR bradycardia, AVJR, and accelerated AVJR. In addition, ECG findings were evaluated for AVB types and QRS axis.

Definition of Study Variables

Severe bradycardia was defined as the presence of admission heart rate ≤40 beats per minute (bpm). Moreover, severe hypotension was defined as the presence of admission systolic blood pressure (SBP) ≤60 mmHg.

Approximate mad-honey consumption amounts were quantified by patients' consumption history. According to the Food and Agriculture Organization and International Network of Food Data Systems Global Food Composition Density Databases; one teaspoon of honey weighs approximately 7.08 g.[17]

Outcomes

Emergency service follow-up time, hospitalization, severe hypotension, and severe bradycardia are considered poor prognostic factors (severity of intoxication), and the population was categorized into two groups; with or without. Moreover, demographic, clinical characteristics, laboratory values, and ECG findings were aimed to analyze for each group.

Furthermore, patients with a history of regular daily intake of mad-honey for more than 1 month are termed as chronic consumers. Moreover, it is categorized into two groups; with or without. Moreover, demographic, clinical characteristics, laboratory values, and ECG findings were analyzed for each group.

Ethics Approval and Consent to Participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee (No: 2013/350). Informed consent was not required, as this study was conducted retrospectively. The study data were evaluated by double-blinded consultant cardiologists (at least post-fellowship experience of 5 years).

Statistical Analysis

SPSS Statistics (17.0; IBM) SPSS, Chicago, IL, USA) used for statistical analysis. The normally distributed data were determined by the Kolmogorov-Smirnov test. Categorical variables were represented as numbers and percentages and continuous variables as medians with 25th and 75th percentiles. Spearsmen correlation test was used for abnormally distributed data. Mann-Whitney U test was used for comparison of median values of two separate groups. Moreover, Chi-square test was used for comparison of categorical variables. Analysis of variance was used to determine different groups, whether or not different from each other. Adjudicated outcomes were tabulated by hospitalization, ischemia likely ECG changes, chronic mad-honey consumption, and poor vital signs. After stratification logistic regression test was applied to evaluate their effect on hospitalization and ischemia likely ECG changes. Binary and multiple logistic regression analysis adjusting for factors, and a validated predictor of hospitalization, poor vital signs, or ischemia likely ECG changes. Logistic regression analysis was performed to assess the odds ratio (OR) and 95% confidence interval (CI) of hospitalization or ischemic ECG changes associated with factors at any time during the admission for MHI. For statistical significance, $p<0.05$ and 95% CI were accepted.

Results

The study population median age was 52.0 years (quartiles 41.00-59.00). The distribution of patients according to gender was 26 females (22.2%) and 91 males (77.8%). The median age of females was 52.5 years (quartiles 44.75-59.25) and males were 51.0 years (quartiles 40.0-59.0).

Baseline demographic characteristics and laboratory findings are listed in the Table 1.

None of the patients had an arrhythmia history. Moreover, according to antiarrhythmic drug consumption, 4 (3.4%) patients were using beta-blockers.

The first 4-month period of the year was significantly more frequent in MHI cases ($p<0.001$). The First 4-month considers 61.5% of (72) patients.

Severe bradycardia incidence was higher in beta-blocker usage patients than patients without ($p=0.03$) (75% of beta-blocker usage patients are also had severe bradycardia).

Fifteen (12.8%) patients had been hospitalized because of prolonged hypotensive and bradycardic effects of MHI for further monitoring. MHI patients were categorized into one of two groups: Those with hospitalization and those without (Table 1). Univariate analysis was used to compare both groups adjusting for confounding factors, using one-to-one match on hospitalization. Moreover, multivariate model adjustment using step-wise selection demonstrated that beta-blocker usage (OR 52.871; 95% CI: 3.618-772.554 [p=0004]), AVJR (OR: 5.319; 95% CI: 1.090-25.949 [p=0.039]), and quantity of mad-honey consumption (OR: 1.035; 95% CI: 1.008-1.063 [p=0.011]) are predictors of hospitalization. ROC curve analysis showed cutoff value of mad-honey consumption quantity of 24.79 g had 57% sensitivity and 68% specificity for predicting hospitalization (AUC: 0.7, 95% CI: 0.55-0.816, p=0.027) (Fig. 1). Hospitalization rates were 52 times higher in patients with beta-blocker usage. Moreover, each unit of mad-honey consumption increases the hospitalization by 3%.

Table 1. Comparison of baseline demographic, clinical characteristics, and laboratory findings for hospitalization

Characteristics	Overall population n=117 (100)		Without hospitalization n=102 (87.2%)		Hospitalization 15 (12.8%)		p
	n	%	n	%	n	%	
Gender, male	91	77.8	76	74.5	15	100.0	0.998
Age (years)*	52.00 (41.00-59.00)		51.00 (41.00-59.00)		57.00 (39.00-60.00)		0.563
Hypertension	24	20.5	22	21.6	2	13.3	0.461
Dyslipidemia	12	10.3	11	10.8	1	6.7	0.624
DM	13	11.1	13	12.7	0	0.0	0.143
CKD	8	6.8	7	6.9	1	6.7	0.978
Previous CAD	5	4.3	4	3.9	1	6.7	0.624
Previous CHF	1	0.9	1	1.0	0	0.0	0.700
BB usage	4	3.4	1	1.0	3	20.0	0.007
Median heart rate (beats/minute)*	45.0 (40.0-50.0)		45.0 (40.0-50.25)		42.0 (38.0-46.0)		0.315
Median SBP(mmHg)*	80.0 (70.00-80.00)		80.0 (70.00-80.00)		70.0 (60.00-80.00)		0.229
Severe hypotension (SBP ≤60mmHg)	28	23.9	23	22.5	5	33.3	0.361
Approximately median quantity of mad-honey consumption (grams)*	21.25 (21.25-43.00)		21.25 (19.477-43.0)		30.16 (21.25-48.188)		0.015
Honey consumption time (hour:minute)*	09:30 (08:00-12:30)		10:00 (08:00-13:15)		07:30 (07:00-09:30)		0.007
Approximate time period of honey intake (days)*	3 (1.0-10.0)		1.0 (1.0-7.75)		2.0 (1.0-90.0)		0.241
Onset of symptoms (hours: minutes)*	1:30 (1:00-2:00)		1:30 (1:00-2:00)		1:00 (1:00-2:00)		0.719
Treatment type							0.998
Saline infusion	17	14.5	17	16.7	0	0.0	N/A
Saline infusion and atropine	100	85.5	85	83.3	15	100.0	N/A
Biochemical results							
Na (mmol/L)*	140.0 (139.0-142.0)		140.0 (138.0-142.0)		141.0 (138.75-143.0)		0.482
K (mmol/L)*	4.2 (3.9-4.4)		4.2 (3.9-4.4)		4.2 (3.9-4.4)		0.514
Creatinine (mg/dl)*	0.95 (0.80-1.16)		0.93 (0.80-1.17)		1.05 (0.79-1.17)		0.859
Glucose (mg/dl)*	100.5 (89.0-114.25)		101.0 (91.0-115.0)		87.50 (71.75-109.25)		0.024
Aspartate transaminase (U/L)*	18.00 (16.00-21.00)		18.00 (16.00-22.00)		19.00 (15.75-20.25)		0.606
Alanine transaminase (U/L)*	17.00 (12.00-22.00)		17.00 (13.00-23.00)		15.50 (11.00-16.00)		0.121
CK-MB (U/L)*	16.00 (12.00-22.00)		16.00 (12.00-21.00)		16.00 (13.25-55.50)		0.241
Peak hscTn-I (ng/ml)*	0.006 (0.006-0.012)		0.006 (0.006-0.011)		0.014 (0.006-0.072)		0.124
hscTn-I positive	5	4.3	3	3.2	2	14.3	0.129

*: Median (25-75th percentiles), Chronic kidney disease-creatinine >2.0 mg/dl, hemodialysis or renal transplantation; DM: Diabetes mellitus; CKD: Chronic kidney disease; CAD: coronary artery disease; CHF: congestive heart failure; BB: beta-blocker; SBP: Systolic blood pressure; Na: Sodium; K: Potassium; hscTn-I: High sensitive cardiac troponin-I.

There was no mortality occurred, even a temporary pacemaker or invasive cardiac procedure was not required. Moreover, all cases were discharged from the hospital without any complication.

According to ECG findings, all patients had bradyarrhythmias. Sinus bradycardia was most commonly demonstrated arrhythmia (91 of 117 patients (77.8%). Main arrhythmia types were sinus bradycardia, AVD (14 (12.0%)),

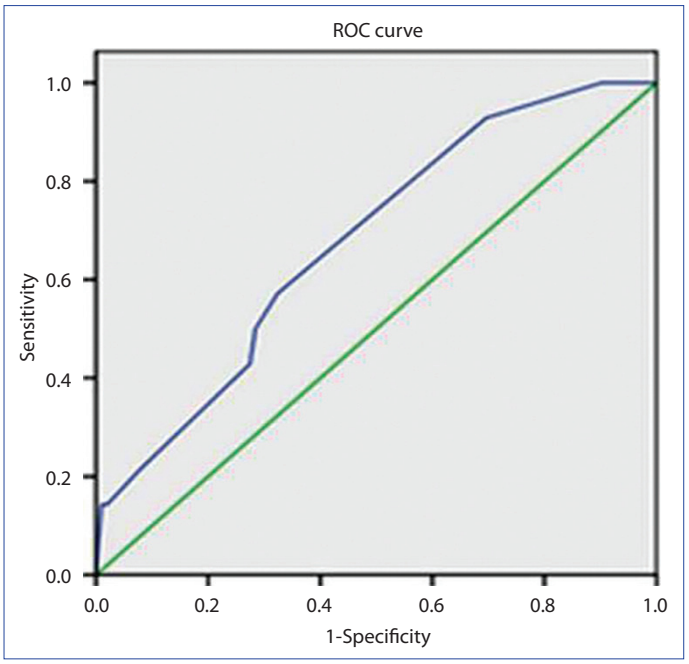

Figure 1. ROC curve analysis demonstrating predictive cutoff value of mad-honey consumption quantity for hospitalization in mad-honey intoxication.

and AVJR (12 (10.3%)). Figure 2 showed isorhythmic AVD. Figure 3 showed AVD "with accrochage." Moreover, AVJR is shown in Figure 4.

Rhythm disturbance in the majority of cases (24 [20.5%]) was 1st-degree-AVB (Table 2). Patients with AVJR had higher hospitalization rates, but not with other arrhythmias. Hospitalization rates were 5 times higher in patients with AVJR.

Fifty-six (47.9%) patients had ischemia likely ECG changes. Moreover, T wave inversion (32 patients (27.4%)) was the most common finding (Fig. 5 and 6). MHI patients were categorized into one of two groups: Those with ischemia likely ECG changes and those without. There was a significant relationship found between AVJR and ischemia likely ECG changes (2 (3.3%) versus 10 (17.9%) p=0.009), but not with other arrhythmias. Furthermore, patients with ischemia likely ECG changes had more intense therapy than without (p=0.03). However, there was no relation found with the previous coronary artery history, gender, demographic characteristics, or poor prognostic factors such as hospitalization, severe bradycardia, or hypotension. There was positive association found between creatinine, glucose, and ischemia likely ECG changes (respectively, z=-2.175; p=0.03, z=-2.084, p=0.037). However, not with hscTn-I levels or troponin positivity.

Only five patients had positive hscTn-I levels. Nevertheless, none of the patients were diagnosed with acute coronary syndrome.

Most of the patients (59 [53.25%]) were consumed mad-honey for the 1st time. Moreover, 22 (19.8%) patients are

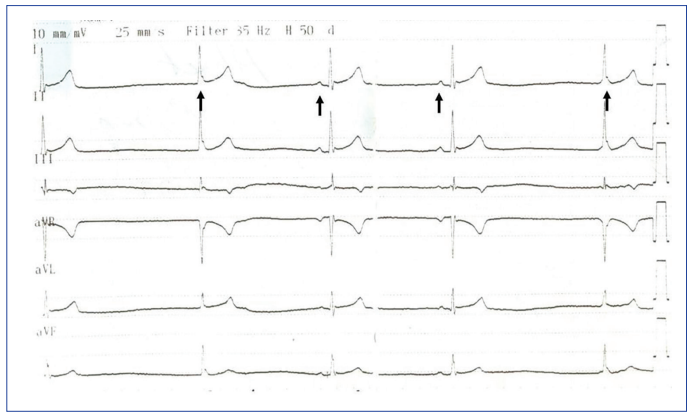

Figure 2. Isorhythmic atrioventricular dissociation, rate 38 bpm. The p waves (arrows) emerge before or after QRS or are hidden in QRS. In one beat, there is likely ventriculoatrial conduction (first arrow).

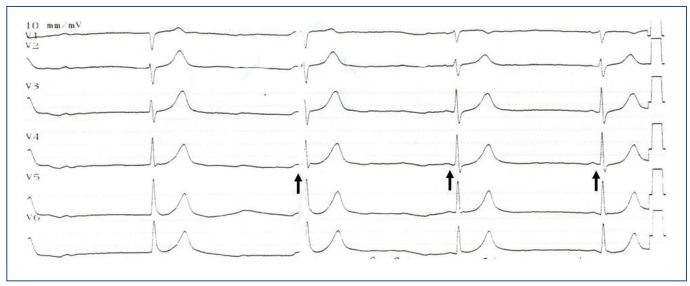

Figure 3. Bradycardic atrioventricular dissociation "with accrochage" rate about 32 bpm. The first beat is an atrioventricular junctional beat, the pQ time of the second p wave is shortened, the third and fourth p waves emerge shortly before QRS complexes.

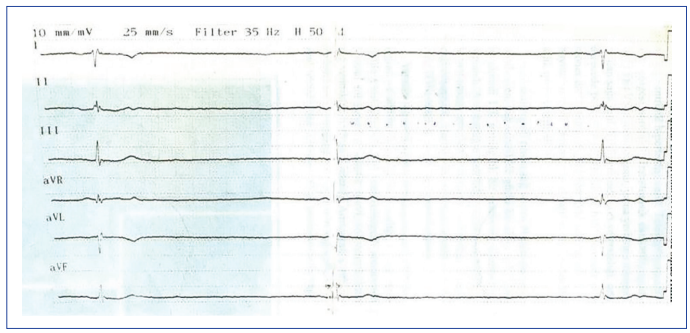

Figure 4. Atrioventricular junctional bradycardia rhythm, rate 20 bpm.

chronic consumers. MHI patients were categorized into one of two groups: Those with chronic consumption and those without. There is no relation was found between chronic consumption and poor prognostic factors (hospitalization, severe hypotension, and bradycardia) or arrhythmias. Even in the chronic consumption group, there was no AVJR, AVD, and 3rd-degree-AVB, sinus arrest was observed. Furthermore, no troponin positivity was observed. Chronic consumers only had sinus bradycardia rhythm (Table 3).

Table 2. Comparison of electrocardiographic findings for hospitalization (Numerical overview of arrhythmia)

	Overall population n=117 (100)		Without hospitalization n=102(87.2%)		Hospitalization n=15 (12.8%)		p
	n	%	n	%	n	%	
Main rhythm types (disturbance)							N/A
Sinus bradycardia	91	77.8	82	80.4	9	60.0	0.076
AVD	14	12.0	12	11.8	2	13.3	0.861
AVJR	12	10.3	8	7.8	4	26.7	0.035
AVD types							0.459
AVD without 3rd-AVB	11	9.4					N/A
AVD with accrochange	7	6.0	6	50.0	1	50.0	N/A
Isorhythmic AVD	4	3.4	4	33.3	0	0.0	N/A
AVD with 3rd-AVB	3	2.6	2	16.7	1	50.0	N/A
AVJR types							0.325
AVJR	8	10.3	6	75.0	2	50.0	N/A
AVJR bradycardia	3	2.6	1	12.5	2	50.0	N/A
Accelerated AVJR	1	0.9	1	12.5	0	0.0	N/A
Admission AVB types							N/A
1st-degree AVB	24	20.5	22	21.6	2	13.3	0.461
2nd-deg type-1 AVB	1	0.9	1		0	0.0	N/A
2nd-deg type-2 AVB	0	0.0	n/a		n/a		N/A
3rd-degree AVB	3	2.6	2	2.0	1	6.7	0.282
Sinus arrest	5	4.3	5	4.9	0	0.0	0.381
Severe bradycardia (≤40 beats/minute)	32	27.4	27	26.5	5	33.3	0.578
QRS axis							0.097
Normal	85	72.6	74	72.5	11	73.3	N/A
LAFB	1	0.9	1	1.0	0	0.0	N/A
Left axis	5	4.3	4	3.9	1	6.7	N/A
Right axis	2	1.7	1	1.0	1	1.0	N/A
Incomplete RBBB	20	17.1	20	19.6	0	0.0	N/A
RBBB	2	1.7	1	1.0	1	6.7	N/A
LBBB	2	1.7	1	1.0	1	6.7	N/A
Ischemia likely ECG changes	56	47.9	49	48.0	7	46.7	0.921
T wave inversion	32	27.4	25	24.5	7	46.7	N/A
ST elevation	16	13.7	16	15.7		0.0	N/A
Biphasic T wave	10	8.5	10	9.8	0	0.0	N/A
ST depression	6	5.1	6	5.9	0	0.0	N/A

AVD: Atrioventricular dissociation; AVB: Atrioventricular block; AVJR: Atrioventricular junctional rhythm; LAFB: Left anterior fascicular block; RBBB: Right bundle branch block; LBBB: Left bundle branch block; ECG: Electrocardiography.

Discussion

MHI cases are observed very rarely in the literature even as case reports. However, in this study, we have reviewed 246 MHI patients in only one medical center, and 1-year period. Even, residents wise to optimal consumption dosage of mad-honey, familiar with the MHI sign, symptoms, and negligence the toxic effects of mad-honey. Moreover, cases often heal spontaneously for this reason rarely encountered in primary medical facilities. Therefore, actual numbers are much more than seem. Even all MHI cases have been alerted about not consuming mad-honey before discharge; unfortunately, three patients come again in 5 months period with MHI. A coordinated set of actions, at the public and individual level, aimed at eradicating, eliminating mad-honey intake is needed for the minimizing of MHI.

Like studies in the literature[2] in our study population, mad-honey consumption was frequently observed in the 5th decade. The reason for these may be patients in 50 decades that were more sensitive to mad-honey, or in 50 decades with

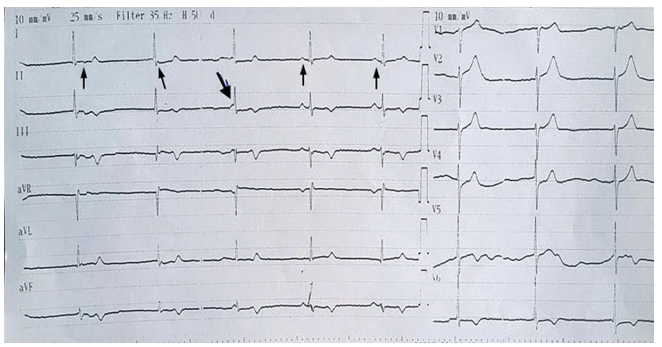

Figure 5. Initial ECG showed atrioventricular dissociation "with accrochage" (42 bpm), and T wave inversion at D2, D3, aVF, V5, and V6 derivations.

ECG: Electrocardiography.

emerging of chronic diseases and aging psychology, patients tend to use alternative therapies more often. Furthermore, the majority of reports are for males.[2] Consistently, in the study population, the male gender accounts for 77.8% of patients. The local population is aware of the negative effects of mad-honey; therefore, females avoid consumption of mad-honey and are observed in fewer numbers.

Although mad-honey is even more toxic during springtime than other seasons,[18] in our study population, MHI cases were more frequently observed in the first 4-month period of the year. This result may be linked to the increased usage of mad-honey against winter flu and upper respiratory tract infections in the winter period. Even, researches on regular honey have revealed its antimicrobial activities.[19,20] Evaluation of the population in two subgroups with first 4-month and other month period patients showed no difference in demographic, clinical, or ECG findings. Hence, the incidence of intoxication in the winter period should only depend on the frequency of mad-honey consumption.

Similar to research results[2,18,21] in our study population, mad-honey is frequently consumed about morning hours (breakfast time) (median mad-honey consumption time was 09:30 (quartiles 08:00-12:30). The approximately median quantity of mad-honey ingestion was 21.25 g (21.25-43.00). Moreover, median time elapsed between ingestion of honey and start of complaints was 1:30 h: min (quartiles 1:00-2:00).

The median admission heart rate was 45.0 bpm (quartiles 40.0-50.0). Median SBP was 80.0 mmHg (quartiles 70.00-80.00). Even, these poor vital signs and arrhythmias were normalized than should be, because saline infusion and/or atropine therapy frequently started at ambulance or first admitted medical center.

MHI cases were followed on the median of 4:17 h: min (quartiles 2:45-6:03) in the emergency room. Patients were more often received saline infusion and atropine therapy 100 (85.5%), and less often received only 17 (14.5%) saline infusion. One hundred and two (87.2%) patients .were discharged from the emergency room after initial evaluation. Patients with severe bradycardia more often received saline

Table 3. Comparison of clinical characteristics and electrocardiographic findings for chronic mad-honey consumption (Numerical overview of arrhythmia)

	Overall population		Without chronic mad-honey n=111 (100) consumption n=89 (80.2%)		Chronic mad-honey consumption n=22 (19.8%)		p
	n	%	n	%	n	%	
1st-degree AVB	23	20.7	17	18.4	6	4.6	0.397
Sinus arrest	5	4.5	5	5.6	0	0.0	0.255
Ischemia likely ECG changes,	53	47.7	45	50.6	8	36.4	0.233
hscTn-I positivity	4	3.9	4	4.8	0	0.0	0.329
Hospitalization	9	8.1	6	6.7	3	13.6	0.289
Severe bradycardia (≤40 beats/minute)	31	27.9	27	30.3	4	18.2	0.255
Severe hypotension (SBP ≤60mmHg)	25	22.5	22	24.7	3	13.6	0.265
Main arrhythmia types							
Sinus bradycardia	87	77.8	85	73.0	22	100.0	0.006
AVD	14	12.6	14	11.2	0	2.8	0.047
AVJR	10	9.0	10	8.0	0	2.0	0.099

AVB: Atrioventricular block; ECG: Electrocardiography; hscTn-I: High sensitive cardiac troponin-I; SBP: Systolic blood pressure; AVD: Atrioventricular dissociation; AVJR: Atrioventricular junctional rhythm.

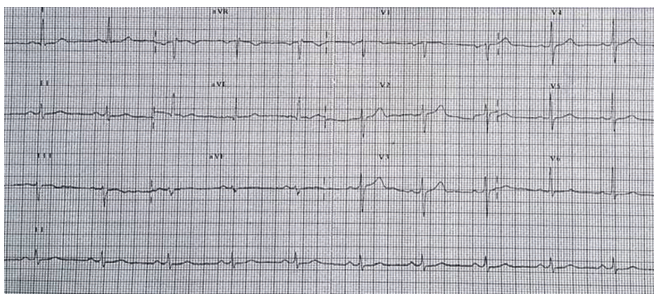

Figure 6. After saline infusion, atropine administration, and regular follow-up, ECG reversed to normal sinus rhythm.

ECG: Electrocardiography.

and atropine therapy (p=<0.001). As expected, emergency room follow-up time was higher in patients with severe hypotension (z=-3.424; p<0.001).

Compatible to the literature findings,[22] there were a linear regression and reverse correlation found between mad-honey ingestion amount and heart rate (F (1.114)=0.026; p<0.001) (r=-0.013). As expected, the clinical effects of MHI depend on consumption dose.

Although there was no difference found between approximately mad-honey consumption amount (males 21.25 g (21.25-43.0) versus females 21.25 g (14.16-28.32) (z=-1.267; p=0.21)) and chronic consumption (intake ≥30 days) between gender (males 16 (18.8%) versus females 6 (23.1%) (p=0.634)), admission heart rate of males was significantly lower than females (44.0 bpm [38.0-50.0] versus 47.5 bpm [43.75-55.25] [z=-2.317; p=0.021]). Moreover, also, all hospitalized cases were male. Even, in clinical characteristics evaluation, females had more frequently had chronic diseases (hypertension and hyperlipidemia [respectively p=0.01, 0.015]). The reason for this may be males are more sensitive to grayanotoxin than females. Even, in some studies, females have less severe symptoms and ECG findings than males.[23,24]

In the literature, some studies were shown the antidiabetic effects of regular honey.[25,26] Similarly, in our study, there was linear regression and reverse correlation was found between mad-honey consumption quantity and glucose levels (F[1.107]=5.018; p=0.027) (r=-0.212). Hence, mad-honey may be had anti-diabetic effects. Moreover, the future studies are needed to firmly determine the influence of mad-honey.

Fifteen (12.8%) patients had been hospitalized. Compatible with the literature, the median time of hospitalization was found 1.0 days (1.0-1.0).[21] However, our findings are incompatible with the literature in terms of lower hospitalization ratio (12.8% vs. 28.45%).[2]

Like literature findings in our study, main rhythm disturbance is sinus bradycardia,[2] and following by AVJR, and AVD. It is the 1st time in the literature, MHI cases are evaluated for AVD types. Even in our study, AVD was observed with a considerable amount. Reverse to the literature finding with a ratio of 45.8%[2] 3rd-degree-AVB observed only in three (2.6%) patients.

MHI generally has a good prognosis; patients are discharged without any complication after a short period of observation. At first glance, MHI seems negligible. On the other hand, overlapping of the symptoms of heart failure, myocardial infarction, or rhythm disorders with MHI undoubtedly contributes to the underdiagnoses of cardiac problems in MHI or vice versa. In addition, our study shows that MHI causes ischemia likely ECG changes in almost half of cases and hospitalization with a ratio of 12.8. Moreover, as shown in our study, MHI can be presented with life-threatening arrhythmias (AVD, AVJR, and severe bradycardia) which are even more important in patients with heart diseases.

MHI patients with the acute coronary syndrome were observed very rarely in the literature even as case reports. However, our study has shown that ischemia likely ECG changes are significantly associated with MHI. Ischemia likely ECG changes in MHI is attributed to bradycardia and hypotension, resulting in a reduced supply of blood to the coronary artery, which leads to secondary myocardial ischemia by some studies.[13,14] However, there was no relation found between ischemia likely ECG changes and severe hypotension even with severe bradycardia (respectively, p=0.488 and 0.295). Hereby, intoxication may have a direct cardiac toxic effect instead of cardiac injury secondary to poor vital signs. These results support the ischemic effects of MHI. However, in our study, cardiac enzyme elevation was observed only in a few cases. Furthermore, some case reports depict the association of acute coronary syndrome with MHI.[12-15] May be ischemia likely ECG findings are related to both pure toxic and secondary effects. As a result of this, antiplatelet therapy is questionable in MHI treatment. Hence, further studies are needed for pathophysiological mechanism ischemia likely ECG changes.

Beta-blocker usage had a higher incidence of severe bradycardia and hospitalization. This result may be caused by the synergistic effects of beta-blockers with grayanotoxin. Therefore, MHI cases with beta-blocker usage require close monitoring. Even though only four beta-blocker usage patients exist in the study, statistical analysis demonstrated some highlights about its effect on hospitalization and severe bradycardia. Larger patient groups are needed to firmly determine the influence of beta-blockers or other bradycardic agents in MHI.

Mad-honey is frequently consumed, especially for the traditional medicine of hypertension, hyperlipidemia, and

diabetes mellitus.[2] However, there is no relation found between chronic consumption and hypertension, hyperlipidemia, and diabetes mellitus history, (respectively, p=0.795, 0.634, and 0.669). Even, in our study population with MHI cases, incidence of hypertension, dyslipidemia, and diabetes mellitus is similar or lower than the overall population.[27-29] Demographic and clinical characteristics were analyzed for each group. There is no relation was found between chronic consumption and poor prognostic factors (hospitalization, severe hypotension, and bradycardia) or arrhythmias. Chronic consumers had almost the same outcomes as patients without chronic consumption. Chronic mad-honey consumers were familiar with side effects and optimal dosages of mad-honey. Therefore, they intake small amounts of mad-honey. Furthermore, Aliyev et al.[16] have shown that long-term consumption may lead to desensitization of cells, which precludes intense symptomatic presentation. Therefore chronic consumers' better outcomes cause bias over 1st-time mistakenly consumers outcomes and also cover up chronic toxicity effects of mad-honey. Even in the chronic consumption group, there was no AVJR, AVD, 3rd-degree-AVB, sinus arrest was observed. Furthermore, no troponin positivity was observed. Chronic consumers only had sinus bradycardia rhythm (Table 3).

Study Limitations

Our study is only a single-center and retrospective study and has the intrinsic limitations of such a design. The absence of echocardiography examination and males exceeding in gender is crucial shortcomings. Furthermore, MHI diagnoses were based on only exposure determined from patients' suspicious honey consumption stories and clinical findings.

Conclusion

According to epidemiologic findings of the study; mad-honey is frequently consumed by the male gender, in the fifth decade, during morning hours (breakfast time), and in the first 4 months of the year.

The main rhythm disturbances in MHI are sinus bradycardia, AVJR, and AVD. Furthermore, ischemia likely ECG changes was significantly accompanied by MHI even independent of hypotension or bradycardia.

Chronic consumers had almost the same demographic and clinical outcomes as patients without chronic consumption.

A novel finding is that the male gender, AVJR, the median quantity of mad-honey consumption, and beta-blocker usage play a crucial role in the prognostic assessment of MHI. Furthermore, admission vital signs are high-risk criteria for MHI prognosis. Our study offers insights into the MHI outcomes. The results for morbidity offer substantial reassurance of the relative safety of MHI.

Disclosures

Ethics Committee Approval: The study was approved by Duzce University, School of Medicine, Clinical Research Ethics Committee (Chairperson of the ethics committee: Hakan Ozhan / Date: 14/01/2013 / decision no: 2013/350).

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