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Mad honey (grayanotoxin) intoxication presenting with syncope, refractory bradycardia and transient renal impairment in a hypertensive patient: A Case Report

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Abstract

Mad honey intoxication is a clinical syndrome arising from the consumption of grayanotoxin-containing honey produced by bees from the nectar of *Rhododendron species*, characterized by bradycardia, hypotension, and syncope. Although primarily endemic to the Black Sea region of Turkey, cases have been reported worldwide, including Nepal, Korea, Japan, Austria, and Germany. We present a 65-year-old male patient with known hypertension on ramipril and amlodipine who was admitted to the emergency department following syncope while walking. On admission, the Glasgow Coma Scale score was 15, blood pressure was 74/35 mmHg, heart rate was 45 beats/min, and electrocardiography revealed sinus bradycardia. Abdominal examination was unremarkable except for suprapubic tenderness, with no guarding or rebound. Brain computed tomography and diffusion-weighted magnetic resonance imaging, performed due to bradycardia and hypotension refractory to 1,000 mL of isotonic fluid replacement, revealed no acute pathology. Further history-taking disclosed that the patient had been consuming small amounts of honey brought from the Black Sea region by relatives—described as medicinal—at breakfast for 2–3 days. Under a preliminary diagnosis of mad honey intoxication, 1 mg of intravenous atropine was administered while fluid therapy was continued; heart rate rose to 95 beats/min and blood pressure to 130/80 mmHg shortly thereafter. Initial biochemistry revealed a glomerular filtration rate (GFR) of 47 mL/min/1.73 m^2, blood urea nitrogen (BUN) of 25.8 mg/dL, and creatinine of 1.59 mg/dL; a urinary catheter was inserted for urine output monitoring, with adequate diuresis. Following cardiology consultation, the patient was admitted to the cardiology ward; heart rate remained 60–65 beats/min and blood pressure approximately 110/70 mmHg throughout follow-up, with no life-threatening bradycardia, hypotension, or rhythm disturbance on electrocardiography. Renal function improved progressively (day 1: GFR 56, BUN 27, creatinine 1.56; day 2: GFR 73, BUN 21, creatinine 1.1), and the patient was discharged with recommendations. This case demonstrates that mad honey intoxication can cause serious cardiovascular manifestations even with low-volume consumption, that the response to atropine carries diagnostic value, and that transient renal impairment—rarely reported in the literature—may develop secondary to hemodynamic instability.

Keywords: Mad honey; grayanotoxin; bradycardia; hypotension; syncope; acute kidney injury; atropine

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Introduction

Mad honey intoxication is a distinctive toxic syndrome resulting from the consumption of grayanotoxin-containing honey produced by bees from the nectar of plants belonging to the family Ericaceae, primarily *Rhododendron ponticum* and *Rhododendron luteum* [1,3]. Grayanotoxins bind to voltage-gated sodium channels in their open state, preventing channel inactivation and maintaining the cell membrane in a state of persistent depolarization [2,3]. This effect leads to conduction disturbances particularly in myocardial and neural tissue; through increased vagal tone and parasympathetic stimulation mediated via M2 muscarinic receptors, sinus node suppression, slowing of atrioventricular conduction, and peripheral vasodilation ensue [2,3,9]. Consequently, patients present with clinical manifestations including hypotension, sinus bradycardia, atrioventricular block of varying degrees, dizziness, syncope, altered consciousness, nausea, vomiting, and diaphoresis [1,3,9].

Mad honey is widely regarded as a medicinal product in traditional medicine in Turkey, particularly in the Black Sea Region, where it is commonly used for conditions such as hypertension, diabetes mellitus, gastrointestinal disorders, and sexual performance enhancement; this cultural practice is the primary reason why intoxication remains a regularly reported cause of emergency department presentation in the region [1,3,4,6,9]. A large systematic review reported that the majority of cases occurred in middle-aged to older men, a distribution attributed to the higher prevalence of hypertension and erectile dysfunction in this demographic [1,4]. The relationship between the amount of honey consumed and the severity of intoxication remains a matter of debate; due to the non-uniform distribution of grayanotoxin within honey, even minimal quantities—as little as a single teaspoon—have been repeatedly shown to cause symptomatic intoxication [1,6,8]. Symptoms typically manifest shortly after ingestion and resolve within one to two days; however, onset may be delayed by several hours depending on the dose [2,5].

Diagnosis relies largely on clinical suspicion; as no laboratory test is available for routine measurement of grayanotoxin levels, a thorough dietary and medical history remains the cornerstone of the diagnostic workup in patients presenting with unexplained bradycardia and hypotension [1,3,6,9]. The most common electrocardiographic finding is sinus bradycardia, frequently accompanied by atrioventricular block of varying degrees [1]. Treatment is primarily symptomatic, consisting of intravenous fluid resuscitation and atropine administration; a rapid and dramatic hemodynamic response to atropine is considered an important clinical clue supporting the diagnosis (1,3,9). In rare cases, life-threatening complications such as complete heart block and asystole may develop, and temporary cardiac pacing may be required in refractory cases [3,4,9].

Although the cardiovascular effects of mad honey intoxication have been well characterized in the literature, data regarding its impact on renal function in humans remain scarce; in large case series, renal function tests have generally been within normal limits, and no fatalities have been reported (1). While animal studies have demonstrated that high-dose grayanotoxin administration can induce proteinuria and hematuria, clinically significant renal dysfunction manifesting as elevated serum creatinine has rarely been documented in human cases [3,9].

In this case report, we present a hypertensive patient who developed syncope following the ingestion of a small amount of mad honey, accompanied by sinus bradycardia and hypotension refractory to intravenous fluid therapy, as well as transient renal dysfunction considered to have developed secondary to hemodynamic instability. We further aim to discuss the critical role of a detailed dietary history in establishing the diagnosis and the clinical significance of the rapid hemodynamic response to atropine, in the context of the current literature.

Case report

A 65-year-old male patient with a known diagnosis of hypertension, receiving ramipril (Delix) and amlodipine (Norvas) as antihypertensive therapy, was brought to our emergency department by emergency medical services following a sudden syncopal episode while walking. History obtained from the patient's relatives revealed generalized weakness over the preceding one to two days. On presentation, the patient was conscious with a Glasgow Coma Scale score of 15. Respiratory examination was normal with oxygen saturation within normal limits. Abdominal examination revealed suprapubic tenderness; there was no guarding or rebound tenderness.

On vital signs assessment, blood pressure was 74/35 mmHg, heart rate was 45 beats/min, and electrocardiography revealed sinus bradycardia without evidence of conduction block or ischemia. A 1,000 mL infusion of isotonic sodium chloride was administered for hypotension and bradycardia; however, no significant improvement in blood pressure or heart rate was observed. Given the possibility of a neurological etiology underlying the syncopal episode, brain computed tomography (CT) and diffusion-weighted magnetic resonance imaging (MRI) were performed, both of which revealed no acute pathology.

Upon repeated and detailed history-taking from the patient, whose persistent bradycardia and hypotension remained refractory to fluid therapy, it was learned that a family member had brought honey from the Black Sea Region—described as medicinal—which the patient had been consuming in small amounts at breakfast for the preceding 2–3 days. Mad honey (grayanotoxin) intoxication was therefore suspected as the underlying etiology. One milligram of intravenous atropine was administered while fluid therapy was continued. Shortly thereafter, heart rate increased to 95 beats/min and blood pressure to 130/80 mmHg; this rapid and dramatic hemodynamic response was considered a significant clinical finding in support of the preliminary diagnosis.

Initial biochemical investigations revealed a glomerular filtration rate (GFR) of 47 mL/min/1.73 m^2, blood urea nitrogen (BUN) of 25.8 mg/dL, and serum creatinine of 1.59 mg/dL. A urinary catheter was inserted to facilitate close monitoring of renal function and urine output; adequate diuresis was maintained throughout. Cardiology consultation was obtained, and the patient was admitted to the cardiology ward for close hemodynamic and rhythm monitoring.

Throughout the patient's follow-up in the cardiology ward,

heart rate remained between 60 and 65 beats/min and blood pressure approximately 110/70 mmHg, with no life-threatening bradycardia or hypotension recorded. Serial electrocardiograms revealed no rhythm disturbances, including atrioventricular block or nodal rhythm. The patient remained hemodynamically stable throughout the observation period and was subsequently discharged in accordance with the recommendations of the cardiology team.

Serial monitoring of renal function demonstrated progressive improvement throughout the patient's hospital course. Biochemistry performed one day after admission revealed a GFR of 56 mL/min/1.73 m², BUN of 27 mg/dL, and creatinine of 1.56 mg/dL. By the second day, GFR had risen to 73 mL/min/1.73 m², BUN had decreased to 21 mg/dL, and creatinine had fallen to 1.1 mg/dL, reflecting marked and progressive recovery of renal function (Table 1). The overall clinical and laboratory course suggested that the mild-to-moderate renal impairment observed at presentation was prerenal in origin and transient in nature, attributable to a hypotensive episode secondary to mad honey intoxication.

Table 1: Temporal changes in hemodynamic and renal function parameters.

Parameter	Admission	Day 1	Day 2
Blood pressure (mmHg)	74/35	~110/70	~110/70
Heart rate (beats/min)	45 (95 post-atropine)	60–65	60–65
GFR (mL/min/1.73 m²)	47	56	73
BUN (mg/dL)	25.8	27	21
Creatinine (mg/dL)	1.59	1.56	1.1

GFR: glomerular filtration rate; BUN: blood urea nitrogen.

Discussion

Mad honey intoxication is an important diagnosis to consider in patients presenting with unexplained bradycardia, hypotension, and syncope, and can be established through careful history-taking [3,6]. In the present case, the initial clinical presentation—bradycardia and hypotension refractory to fluid therapy, accompanied by syncope—was largely consistent with typical cases of mad honey intoxication reported in the literature. In a series of 15 cases following the consumption of honey sourced from Nepal, hypotension and bradycardia were present in all patients at admission, and the clinical features and outcomes were noted to be similar to those reported from the Black Sea Region of Turkey; this supports the view that mad honey intoxication exhibits a consistent clinical phenotype regardless of geographic origin [7].

When compared with similar cases reported in the literature, our case may be evaluated from three main perspectives: clinical presentation and diagnostic process, response to treatment and hemodynamic course, and the effect on renal function.

1. Clinical Presentation and Diagnostic Process

The fact that our patient was a 65-year-old man with hypertension is consistent with the typical demographic profile of mad honey intoxication reported in the literature. A large systematic review of 1,199 cases reported that 75.17% of patients were male and 83.19% were between the ages of 41 and 65; in a series of 21 cases by Demircan et al., 85.7% of patients were male with a mean age of 55 ± 11 years (1,4). This gender distribution has been attributed to the higher prevalence of hypertension and erectile dysfunction in middle-aged and older men, and to the traditional use of mad honey for these conditions; some authors have reported that men are affected approximately five times more frequently than women [1,4,9]. Furthermore, the already reduced sympathetic compensatory reserve in patients receiving antihypertensive therapy, when combined with the vagotonic effect of grayanotoxin, may predispose to more severe hemodynamic disturbance; in our case, concomitant use of a calcium channel blocker (amlodipine) may similarly have contributed to the severity of bradycardia and hypotension [2].

The most critical step in the diagnostic process was detailed and repeated history-taking. Normal findings on neurological imaging (brain CT and MRI) suggested a cardiovascular or metabolic etiology underlying the syncopal episode; however, the key to establishing the diagnosis was the identification of the patient's history of consuming honey sourced from the Black Sea Region through targeted questioning. This confirms a point frequently emphasized in the literature: as no routine laboratory test is available to confirm grayanotoxin levels, the diagnosis relies primarily on integrating the geographic and epidemiological history with clinical findings [3,9]. Notably, the patient's consumption history—small amounts of honey consumed at breakfast over two to three days—is consistent with the concept of "chronic mad honey intoxication syndrome" described in the literature, characterized by sinus bradycardia, first- or second-degree atrioventricular block, dizziness, and presyncope, and considered to develop secondary to low-dose, repeated consumption for therapeutic purposes [2]. In some reports, diagnosis has been confirmed by melissopalinological analysis (pollen analysis) of the suspected honey; however, this method is not widely available in routine emergency practice, and in our case the diagnosis was established on clinical grounds alone, without the need for such confirmatory testing [5].

2. Response to Treatment and Hemodynamic Course

In our case, the rapid resolution of bradycardia and hypotension—refractory to fluid resuscitation—following the administration of 1 mg of intravenous atropine alongside continued fluid therapy represented both a therapeutic and diagnostic maneuver. Atropine is well established as the first-line agent in the treatment of mad honey intoxication, antagonizing the excessive vagal tone induced by grayanotoxin and producing marked improvement in heart rate and blood pressure, typically within minutes [3,9]. In a review of 1,199 cases, 79.26% of patients received atropine—most commonly at a dose of 1 mg (49.73%)—and 65.35% received intravenous fluid therapy; only 14.90% required intensive care unit admission, and the majority (71.55%) were discharged within 12 hours [1]. In the series by Demircan et al., most patients achieved complete clinical recovery within 18–48 hours, and dopamine infusion was required in only one patient who failed to respond to atropine [4]. In a multicenter study of 47 patients, all received atropine at doses of 0.5–2 mg, and although the in-hospital observation period varied considerably across centers—ranging from 3.6 to 22.2 hours—no difference in complications or mortality was identified between brief emergency department observation and a one-day inpatient stay [6]. These findings are broadly consistent with the rapid and dramatic hemodynamic response to atropine observed in our case.

A notable feature of our case is that the rapid hemodynamic improvement achieved following atropine administration was

largely maintained throughout follow-up in the cardiology ward. Heart rate remained between 60 and 65 beats/min and blood pressure approximately 110/70 mmHg; while these values reflect a marked improvement compared to the severe bradycardia and hypotension present on admission, no life-threatening bradycardia or hypotension was observed during the follow-up period. This course suggests that the acute effects of grayanotoxin can be largely controlled with a single dose of atropine and supportive therapy, and that hemodynamics normalize gradually as toxin absorption ceases [2,3]. Large series have reported that the majority of cases do not require intensive care and can be safely managed at the ward level; a six-hour observation period may be sufficient for hemodynamically stable patients [1,6,9]. In our case, the severe hemodynamic compromise at presentation, together with the patient's advanced age and history of hypertension, were taken into consideration; however, given the rapid response to atropine and fluid therapy, the patient was admitted directly to the cardiology ward and managed with close hemodynamic and rhythm monitoring—an approach reflecting individualized risk assessment consistent with current literature. The absence of conduction abnormalities on serial electrocardiograms throughout the follow-up period indicates that the patient followed a low-risk clinical course and that conservative management without invasive interventions such as temporary pacing was sufficient to achieve clinical recovery.

3. Effect on Renal Function

The most distinctive finding of our case in terms of its contribution to the literature is the marked and progressive recovery of the mild-to-moderate renal impairment detected at presentation (GFR 47 mL/min/1.73 m², creatinine 1.59 mg/dL), with near-normalization by day 2 (GFR 73 mL/min/1.73 m², creatinine 1.1 mg/dL). This finding is particularly noteworthy in the context of the existing literature; the most comprehensive systematic review to date, covering a 34-year period and analyzing 1,199 cases, reported that renal and hepatic function tests were generally within normal limits, and no case of renal dysfunction documented as elevated creatinine was identified [1]. Animal studies have demonstrated that high-dose grayanotoxin-I administration can induce proteinuria and hematuria without histological parenchymal changes at the renal level, and significant structural alterations—including elevated transaminases—in the accompanying hepatic tissue; however, documented renal dysfunction in the form of elevated serum creatinine remains extremely rare in human cases and has not been specifically investigated in clinical case series [3,9]. In this respect, the renal impairment observed in our patient—which resolved promptly with hemodynamic stabilization—represents a rare, quantitatively documented example of prerenal involvement secondary to mad honey intoxication in a human case.

The clinical course of renal dysfunction in our case supports the notion that it arose not from the direct nephrotoxic effects of grayanotoxin, but from a prerenal mechanism secondary to intoxication-induced hypotension and hypoperfusion. The preservation of urine output throughout the hospital course, together with the rapid return of creatinine and BUN levels to near-normal values within 48 hours following volume replacement and hemodynamic stabilization, is indicative of functional prerenal impairment rather than structural renal injury such as acute tubular necrosis. This finding is clinically significant in demonstrating that renal function should be routinely monitored in patients presenting with mad honey intoxication—particularly those with marked hypotension at admission—while also suggesting that such impairment is largely reversible with hemodynamic recovery.

In conclusion, the comparison across these three dimensions underscores the importance of thorough history-taking in the diagnosis of mad honey intoxication, atropine administration in its treatment, and comprehensive assessment of both cardiac rhythm and renal function during follow-up. Our case supports the view that even low-dose consumption over several days—particularly in elderly patients receiving antihypertensive therapy—can result in significant hemodynamic instability; nevertheless, favorable clinical outcomes can be achieved with prompt symptomatic treatment and close monitoring.

Conclusion

Mad honey intoxication must always be considered in the differential diagnosis of patients presenting with unexplained bradycardia, hypotension, and syncope—particularly those with a history of honey consumption from the Black Sea Region—yet may present with a consistent clinical picture and prognosis regardless of geographic origin [3,7]. This case demonstrates that thorough and targeted history-taking is the cornerstone of the diagnostic process; that a rapid hemodynamic response to atropine represents an important clinical finding supporting the diagnosis; and that renal impairment developing secondary to hemodynamic instability is generally reversible with appropriate fluid resuscitation and hemodynamic stabilization. Raising awareness among emergency physicians regarding mad honey intoxication in patients from or with connections to endemic regions, together with education of the public and primary care providers about the potential risks of mad honey consumption, is essential for preventing delayed diagnosis and the performance of unnecessary investigations or interventions [8].

Conflict of Interest: The authors declare no conflict of interest related to this study.

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