Mad Honey Poisoning: Another Substance causing Muscarinic Overactivity

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Abstract

Mad honey syndrome is the poisoning by Grayanotoxin, produced by plants of genus* Rhododendron *of Ericacea family. Grayanotoxin poisoning is relatively uncommon and is encountered mostly in Nepal and Turkey, where the plants are found in abundance. The similarity between the symptoms of Grayanotoxin toxicity and organophosphate compounds (OPC) poisoning poses the challenge of differentiating between the two, and a possibility of atropine poisoning while treating as OPC poisoning. Here we report the first ever case of "Mad Honey Syndrome" in Bangladesh, where meticulous history taking helped us in proper diagnosis and appropriate management.

Key words: Mad honey, grayanotoxin, muscarinic overactivity

(J Bangladesh Coll Phys Surg 2024; 42: 383-386)
DOI: https://doi.org/10.3329/jbcps.v42i4.76300

Introduction

Honey is a natural food produced by honeybees from the nectar of plants which can be consumed unprocessed.[1] Mad honey is honey containing a compound named grayanotoxin, which is produced by plants of Ericaceae family, especially by the genus *Rhododendron*.[2] Consumption of mad honey or grayanotoxin can cause serious adverse effects and is termed as 'mad honey poisoning'.[1] Grayanotoxin poisoning is relatively uncommon and is encountered mostly in Nepal and Turkey where the plant is found in abundance.[2] Mad honey is utilized for conditions other than that of common honey, such as hypertension, peptic ulcer disease, and also as a sexual stimulant.[3] Mad honey can be potentially lethal if left untreated; however, no fatal case has been reported since mad honey poisoning has been defined medically in 1983.[4] Here, we describe the first-ever case of "Mad Honey Syndrome" in Bangladesh, for which a thorough history taking was crucial to the correct diagnosis and course of treatment.

Case Report

A 42-year-old man came to the emergency with an acute onset of abdominal pain and bloating, vomiting, history of fall and drowsiness. There was no history of diarrhea, chest pain, headache, weakness or convulsion. He did not have any comorbidities and was not on any regular medication.

On examination at the emergency department, he was found severely dehydrated. His pulse was 38/min, blood pressure was non-recordable, Oxygen saturation (SpO_2) was 98% in room air, respiratory rate was 18/min, and Glasgow Coma Score was 15/15. His plantar response was flexor bilaterally and his pupils were 3 mm, equal in both eyes and were reacting to light. On auscultation of the lungs there was vesicular breath sound and was no added sound.

His ECG (Figure 1) revealed sinus bradycardia with a rate of 38 beats per minute. Complete blood count and electrolytes were within normal limit. But his creatinine was 1.8 mg/dl (normal 0.6-1.2 mg/dl) and Troponin I was 0.061 ng/ml (normal <0.034ng/ml), which were slightly raised.

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Received: 06 February, 2024 **Accept:** 13 March, 2024

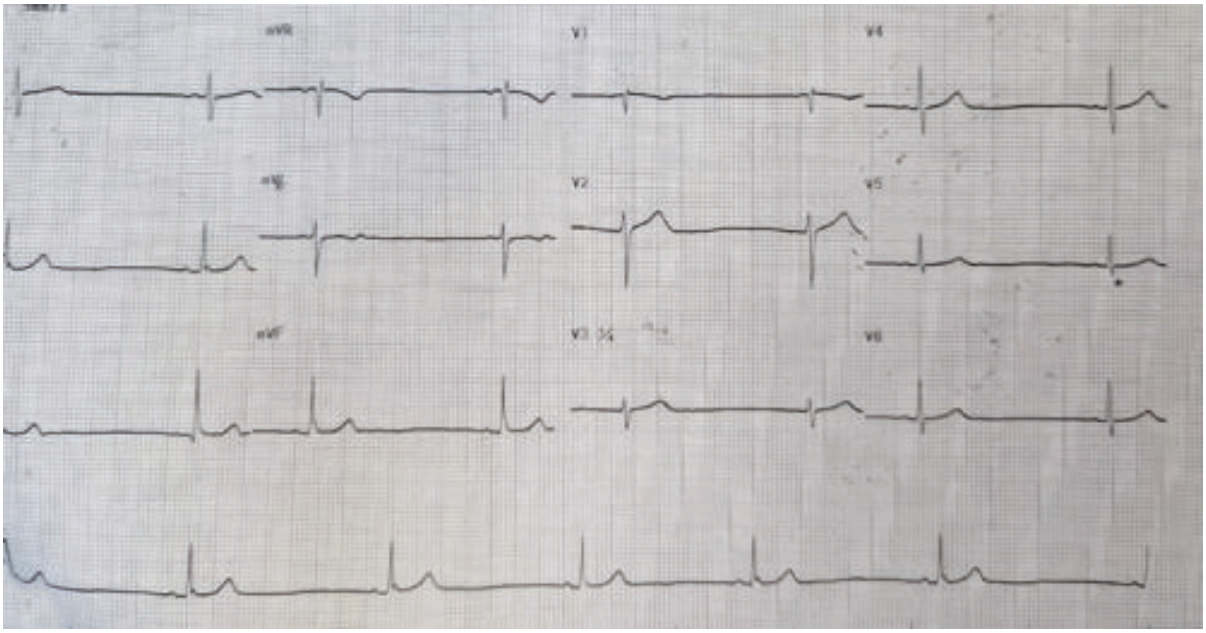

Figure 1: *ECG showing sinus bradycardia*

He was immediately resuscitated at the ER with 1.2 mg atropine intravenously and IV crystalloid fluid challenge with 500 ml of 0.9% sodium chloride, which corrected the bradycardia and temporarily restored normal blood pressure. He was then shifted to the department of Acute Medicine for further management. He was managed with vasopressor support for the next 12 hours along with IV 0.9% sodium chloride. After his hemodynamics were stable, on further query he gave history of ingestion of a special honey that he had brought from Nepal, the mad honey. He admitted that he consumed about 25ml of that honey at one go. After stabilization of his vitals, he was observed for 24 hours and then discharged home.

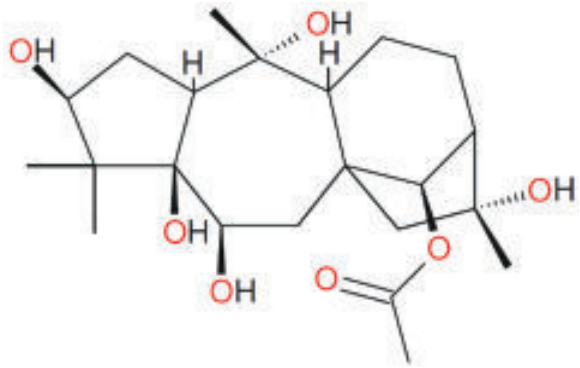

Figure 2: *Structure of grayanotoxin I (adapted from Cardiovasc Toxicol. 2012:12(3))*

Discussion:

Grayanotoxin is produced by plants of Ericaceae family, specifically the genus Rhododendron. Species having high concentrations of grayanotoxin are *R. ponticum, R. flavum and R. luteum*. These speciesare found abundantly in Nepal and in Black Sea regions of Turkey. The toxin is produced by the plant's stem, flowers, leaves, pollen and nectar, and can also be found in secondary plant products, such as honey. Several grayanotoxin isoforms have been found from different species of Rhododendron, but grayanotoxin I and III are assumed to be the principle toxic isoforms. Structurally grayanotoxins are diterpenes, which are polyhydroxylated cyclic hydrocarbons without nitrogen.[2]

The toxin binds to the voltage gated sodium channels on the cell membranes of neurons preventing inactivation of the channel, resulting in prolonged depolarization and ultimately leading to vagal activation, inducing bradycardia and hypotension.[2] Grayanotoxin also has other effects on muscarinic receptors.[3]

The symptoms of mad honey poisoning are dose dependent. In mild form there is dizziness, impaired

consciousness, excessive perspiration, nausea, vomiting, hypotension. However, severe intoxication may lead to life threatening cardiac complications including complete heart block.[4] However, diplopia, blurring of vision, diarrhea, excessive salivation, dyspnoea have also been reported.[1] Among all the symptoms, sinus bradycardia and hypotension are the most frequently reported presentation of mad honey poisoning.[5]

The onset of symptoms occurs few hours after ingestion of the honey and lasts for about 24 hours in most cases.[6] There was no case fatality reported to date.

Mad honey poisoning was first described by Xenophon, a Greek military leader and a historian, in 401 BC in his diary named Anabasis. He described an episode of mad honey poisoning that his soldiers suffered while traveling through the Black Sea regions of Turkey. His journal described the symptoms which were vomiting, diarrhea, prostration and loss of coordination, and also the relation of the amount taken with the appearance of symptoms and the approximate time of recovery. He also reported that there was no fatality.[7] However, in 69 BC, the army of Pompey the great, suffered a defeat to king Mithridates VI of the kingdom of Pontus in northern Anatolia, owing to poisoning by mad honey. King Mithridates used his knowledge of the intoxicating property of mad honey, which he gathered from his adviser the Greek physician Kateuas. When Pompey attacked in 67 BC, he retreated to the southern shores of Black Sea over the course of a year, where the honey was found and deliberately tricked the advancing army into consuming the honey, which left them unable to fight back and thus many were killed by king Mithridates' soldiers.[8]

Mad honey poisoning has presentation similar to cholinergic toxicity, although not a classic cholinergic toxidrome.[3] As grayanotoxin has muscarinic effects, its toxicity presents with symptoms like those of organophosphorus compound (OPC) poisoning, which is very common in Bangladesh.[9] Poisoning by both grayanotoxin and OPC causes hypotension, bradycardia, vomiting, diarrhea, sweating, diplopia. But OPC has a characteristic smell, which is obvious when taken in lethal amount, and its poisoning causes miosis and bronchorrhea which is not found in grayanotoxin intoxication.[1,10]

Regarding the management of poisoning of grayanotoxin and OPC there is also similarity. Antidote to both is atropine. But the difference lies in the dose of the drug. While OPC poisoning needs atropinization with a large amount of atropine and then a maintenance dose,[10] symptoms of grayanotoxin poisoning wears off usually within 24 hours, only the bradycardia needs reversal which requires 0.5-1 mg of atropine, but may require a temporary pace maker.[4]

If grayanotoxin poisoning is mistaken as OPC poisoning and atropine is administered in an amount more than required, it may cause atropine poisoning, resulting in life threatening tachycardia and hypertension.[11]

The physicians from Bangladesh are at home with the symptoms of OPC poisoning and have all the tools necessary to handle a case effectively. However, grayanotoxin poisoning might be misdiagnosed as OPC poisoning because it is a novel form of poisoning with comparable symptoms. In such situation there is risk of overdose of atropine which may lead to atropine poisoning.

Although mad honey is not readily available in Bangladesh, people from Bangladesh are frequently travelling to Nepal and Turkey, where it is easily found. Grayanotoxin lacks the characteristic smell of OPC; nevertheless, proper history and meticulous clinical examination is the key to differentiating between intoxication by these toxins.

Conclusion:

Mad honey poisoning is rare and is usually confined to distinct geographical locations. But in this era of globalization, it is fascinating how accessibility has expanded making everything available everywhere, rendering such exotic things no longer enclosed in their native region. Therefore, for the diagnosis of mad honey poisoning it is crucial to have a high index of suspicion.

Conflict of interest: None declared.

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