Chronic mad honey intoxication syndrome: a new form of an old disease?

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Aims
Although cases of acute mad honey intoxication have been reported earlier, chronic mad honey intoxication (CMHI) syndrome has not been described and we address this issue only in this study.

Methods and results
We prospectively evaluated the history of non-commercial honey intake in all patients referred to our institution for investigation of slow heart rate or atrioventricular (AV) conduction abnormalities. Between April 2008 and December 2008, 173 patients were referred to our institution for assessment of sinus bradycardia and various degrees of AV block and/or permanent pacemaker implantation. All patients were questioned about history of honey intake. Detailed evaluation revealed a history of daily honey intake for a long period of time in five of the patients (2.8%). This non-commercial honey was made by different amateur beekeepers in eastern Black Sea region of Turkey. Discontinuation of honey intake resulted in prompt normalization of conduction and significant symptomatic improvement. None of the patients were admitted to hospital and all were asymptomatic during 3 months follow-up. Holter monitoring for 24-h revealed no abnormality at first and third month.

Conclusions
This is the first report of CMHI. This issue should be suggested during assessment of patients with unexpected conduction abnormalities, because abandonment of honey intake results in prompt symptomatic and electrocardiographic improvement.

Keywords
Chronic • Intoxication • Mad honey

Introduction
Previous reports concerning mad-honey poisoning, generally described various degrees of atrioventricular (AV) block, sinus bradycardia, asystole, convulsion and even acute myocardial infarction.1–5 A review of medical literature will reveal a huge number of cases with acute mad honey intoxication generally presenting within first 24 h after ingestion of mad honey. Despite this great number of patients with acute intoxication, none of the reports present data about chronic honey intoxication. In our experience, we observed several cases with a history of regular daily intake of non-commercially produced honey and various degrees of AV conduction abnormalities. Based on this observation we planned to evaluate this issue prospectively.

Methods
The methodology of this study was very simple. We investigated the history of honey intake in all patients referred to our centre for investigation of bradycardia, slow heart rate, AV conduction abnormality, and/or implantation of permanent pacemaker. Patients’ electrocardiograms were reviewed by two experienced electrophysiologists.

Results
Between April 2008 and December 2008, 173 patients were referred to our institution for investigation of bradyarrhythmia and/or permanent pacemaker implantation. Of this, 109 patients (63%) have undergone permanent pacemaker implantation.
Five patients (2.8%) had a history of ongoing honey (non-commercially produced) intake for at least last 3 months. Clinical and electrocardiographic characteristics of these 5 patients are presented in Table 1. All the patients had various degrees of AV conduction abnormality together with narrow QRS complexes. None of the patients required hospitalization. Cessation of honey intake resulted in rapid symptomatic and electrocardiographic improvement. Assessment of 24-h Holter monitoring revealed no abnormality after 1 and 3 months of follow-up.

### Table 1 Clinical and electrocardiographic characteristics of patients with suspected chronic honey intoxication

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Age</th>
<th>Gender</th>
<th>ECG abnormality</th>
<th>Symptoms</th>
<th>Approximate duration of honey intake (months)</th>
<th>Approximate daily amount of honey intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>Female</td>
<td>SB, type II second degree AV block</td>
<td>Dizziness, presyncope</td>
<td>&gt;12</td>
<td>3–5 teaspoons</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>Male</td>
<td>2:1 AV block</td>
<td>Dizziness, presyncope</td>
<td>3</td>
<td>3–5 teaspoons</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>Female</td>
<td>SB, type I second degree AV block</td>
<td>Dizziness, presyncope</td>
<td>&gt;12</td>
<td>&gt;5 teaspoons</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>Male</td>
<td>SB, type I second degree AV block</td>
<td>Dizziness, presyncope</td>
<td>&gt;12</td>
<td>~10 teaspoons</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>Male</td>
<td>SB, type I second degree AV block</td>
<td>Dizziness, presyncope</td>
<td>&gt;12</td>
<td>3–5 teaspoons</td>
</tr>
</tbody>
</table>

All the patients had narrow QRS complexes. AV, atrioventricular; ECG, electrocardiogram; SB, sinus bradycardia.

**Discussion**

This is a first prospective study investigating chronic mad honey intoxication (CMHI). As it was shown here, 2.8% of patients presenting for assessment of bradyarrhythmia may have CMHI. Whether this effect has a different underlying mechanism when compared with acute intoxication is not clear. Most of the cardiac conduction abnormalities in patients with mad honey intoxication are attributed to the effect of various types of grayanotoxins (GTX), which are present in these kind of honeys.

GTXs are a family of lipid-soluble toxins, which are present in the honey produced from the nectar of Rhododendron species and are responsible for the clinical manifestations of mad-honey intoxication syndrome. Eighteen different types of GTXs have been described. GTX I is the main toxin responsible for cardiac manifestations. These biological toxins act on ion channels and have the capability of modifying the function of these channels. GTXs are classified as toxins binding to site 2 of the Na channels and have unique actions on these channels, such as causing a shift in Na channel activation to hyperpolarizing transmembrane potentials, the elimination of Na channel inactivation, and binding to Na channel in its open state. These toxins require repetitive rather than single, long-lasting, depolarizing stimuli to modify Na channels in excitable cells. Another possible mechanism of GTX toxicity is suggested to be via muscarinic M2 receptors. This point of view is supported by effectiveness of atropine in cases of honey intoxication.

GTX II has the ability to suppress the spontaneous beating of the sinoatrial node. The possible mechanism of this effect was attributed to depolarization caused by GTX II, owing to inflow of Na ions, which in turn produces inactivation of the slow inward current and as the slow inward current becomes small, the activation of the outward current may be reduced. GTX III is a tetracyclic diterpenoid and is the main toxic component obtained from the leaves of Leucothoe grayana MAX. It has been shown on feline cardiac Purkinje fibres that possible mechanism underlying GTX III-induced arrhythmias is the production of triggered activity in the form of oscillatory afterpotentials.

Presence of narrow QRS complexes during various degrees of AV block in all of our patients, suggest that conduction within His–Purkinje system was not affected by GTXs. But it must be noted that various types of GTXs may have different effects (for example GTX II mainly affects sinus node, while GTX I may affect both sinus node and AV conduction). In addition the effects of GTXs through muscarinic receptors may be responsible for the presence of supra-His conduction abnormality (narrow QRS complexes during AV block), and may explain effectiveness of atropine in patients with mad honey intoxication. In Turkey, mad honey is made and widely used in the eastern Black Sea region. But it should be noted that only honey produced from the nectar of Rhododendron species has toxic properties. Honey is frequently consumed during breakfast, but is also believed to be useful in the treatment of gastric pains, colds, various types of viral infections, oral ulcers, bowel disorders, and hypertension, and it is frequently abused as sexual stimulant. With increasing amount of acute ingestion, toxic effects appear to be more severe, but it should be noted that GTXs are not homogeneously distributed within honey, and that is why the level of ingestion should not be used as a criterion of disease severity. GTXs are metabolized and excreted within 24 h after intake. Here, we speculate that during long-term consumption, various degree of desensitization may occur, which itself prevents dramatic symptomatic presentation. Most of the patients complain of generalized weakness. Weakness in turn leads to increased mad honey consumption, because of its well-known ‘therapeutic’ properties.

**Conclusion**

CMHI is an important clinical entity, and should be questioned in all patients undergoing investigation of various types of bradyarrhythmias. Implantation of pacemakers may be avoided easily and symptomatic improvement achieved, simply by discontinuation of honey consumption. This issue may be even more important in the so-called ‘endemic’ countries, where amateur beekeeping is well.
established. But we suggest that clinicians from other countries should also be aware of this special condition, because growing interest on organic products may result in increased numbers of cases of mad honey intoxication in their homeland. But it is also important to realize that commercially produced honey is safe. During commercial production, massive quantities of honey obtained from different farmers undergo excessive processing, and these large quantities of product result in dilution of any toxic substances.

**Conflict of interest:** none declared.

**References**