A 2-Year-old Girl With Bradycardia and Lethargy: Is Perseus to the Rescue?

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CASE

A two-year-old, 13-kg, girl without significant medical history, and prescribed no medications, is brought to the emergency department (ED) with the chief complaint of nausea and vomiting. Prior to ED presentation, she was witnessed to have ingested several leaves from a known, flowering shrub described as green and round on her family's property. Shortly after eating lunch, she developed several episodes of blood-tinged emesis containing bits of leaves.

Upon arrival to the ED, the girl's vital signs are: heart rate, 71/min; blood pressure, 111/92 mmHg; room air pulse oximeter measurement, 100%; and respiratory rate, 20/min. The girl is episodically lethargic and combative with gurgling breath sounds. Intravenous (IV) access is obtained, and a 500 ml normal saline bolus is administered. A finger stick blood glucose measures 77 mg/dl and 2.5 mg dextrose IV is administered. She is also administered 0.25 mg atropine IV for bradycardia.

Due to continued altered mental status and increased oral secretions the girl is endotracheally intubated. Repeat vital signs include: blood pressure, 94/79 mmHg; heart rate, 185/min; respirations, 20/min; and pulse oximeter on ventilatory support, 100%. An electrocardiogram (ECG) obtained after intubation reveals: Sinus tachycardia, 143 bpm; PR interval, 116 ms; QRS, 64 ms; and QT, 450 ms (Fig. 1). The child is administered a midazolam infusion for sedation. Diagnostic testing–including serum electrolytes and serum digoxin concentration–is unremarkable. The child is transferred to a regional pediatric intensive care unit and medical toxicology center. Plant material is brought to the hospital by the parents for identification (Fig. 2).

Can you pick your poison?

Authors interested in submitting a case study in pediatric poisoning for the *Pediatric Emergency Care* feature *Pick Your Poison* are encouraged to contact the Associate Editor, Kevin C. Osterhoudt, MD, via e-mail at OsterhoudtK@email.chop.edu.

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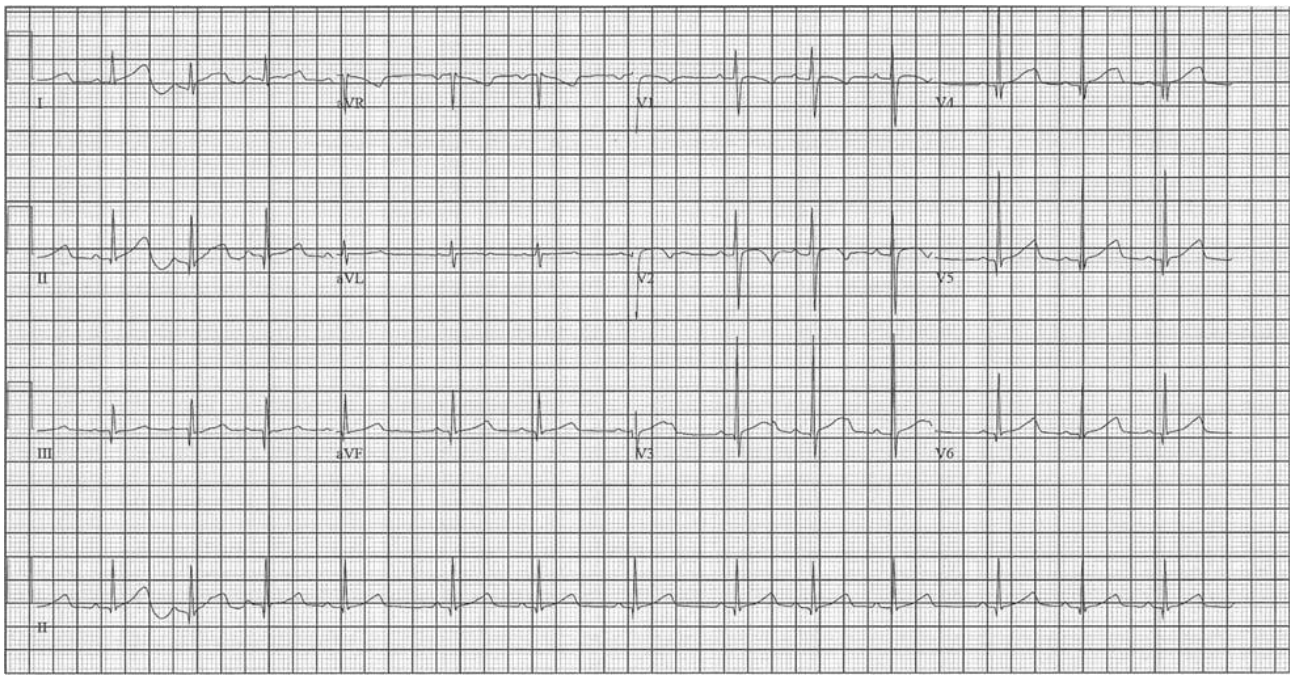

FIGURE 1. Electrocardiogram after endotracheal intubation (see text for interval measurements).

DISCUSSION

According to Krenzelok, et al., in the American Association of Poison Control Centers Toxic Exposure Surveillance System (AAPCC TESS) database, between 2000 and 2009, children younger than five years of age accounted for 81.2% of plant exposures.[1,2] In a 2012 analysis of the database, the top three categories for single substance plant exposures among alleged groups were categorized as: "unknown," "unspecified" or "unidentified."[3] The top six identifiable toxic plants in descending order consisted of: 1) *Phytolacca americana* (pokeweed, or pokeberry), 2) *Spathiphyllum* (i.e., peace lily) species, 3) *Ilex* (i.e., holly) species, 4) *Philodendron* species, 5) *Malus* (i.e., apple, crab apple) species, and 6) cardiac glycoside-containing plants such as *Digitalis* species (i.e., foxglove) and *Nerium oleander* (common oleander).[3]

In the case described above, a two-year-old girl was transported to the ED with acute gastrointestinal signs and symptoms, bradycardia and encephalopathy following an ingestion of leaves of a common outdoor plant. While gastrointestinal disturbance after plant ingestion is nonspecific, cardiotoxicity is less common and thus narrows the differential diagnosis. Diaz categorizes these plants into three distinct groups–cardiac glycosides, sodium channel openers, and sodium and calcium channel blockers.[4]

Cardiac glycosides are some of the more commonly ingested cardiotoxic plants.[3] Examples include: *Nerium oleander* (Common Oleander), *Convallaria majalis* (Lily of the Valley), *Digitalis purpurea* (Foxglove), *Drimia maritime* (Red Squill) and *Apocynum cannabinum* (Dogbane). Cardiac glycosides reversibly inhibit the Na^{+}/K^{+} ATPase in cardiac myocytes, which indirectly increases intracellular Ca^{++} concentration. After ingestion, nausea and vomiting with hyperkalemia, abnormal cardiac conduction, and automaticity disturbances may occur. While this patient did exhibit some signs and symptoms consistent with cardiac glycoside poisoning such as bradycardia, the digoxin concentration was undetectable and neither hyperkalemia nor classical ECG abnormality was observed. Of note, glycoside plants possess varying cross reactivity to digoxin assays and an undetectable or low level does not completely obviate toxicity.[5] Further, the plant description did not match common glycoside plants.

Taxine alkaloids, derived from the yew plant, comprise the class of sodium and calcium channel blockers. Examples include: *Taxus cuspidata* (Japanese yew), *Taxus baccata* (English yew) and *Taxus chinensis* (Chinese yew). Clinical manifestations may include: dizziness, nausea, vomiting, initial tachycardia followed by bradycardia, hypotension, prolongation of

FIGURE 2. Andromeda plant (*Pieris japonica*).

QRS interval and convulsions. This patient did not develop ECG interval abnormalities. In addition, the plant ingested was identified as leafy green; yew plants are a coniferous tree or shrub with needle-like leaves.

Grayanotoxins (GTX)–also known as andromedotoxins or rhodotoxins–fall under the category of sodium channel openers. Grayanotoxins are derived from the leaves, twigs or flowers of plants belonging to the Ericaceae family, such as *Rhododendron*, *Kalmia*, *Agarista* and the *Pieris* genera.[6] The most frequent reported cases of GTX toxicity are from "mad honey disease," which is mainly produced when bees create honey from nectar of nearby rhododendron species[6]; however, direct ingestions by animals and humans have been documented.

Grayanotoxins are diterpenoid alkaloids that have significant effects on the nervous system. There are greater than 25 GTX isomers in Rhododendron.[7] Grayanotoxins 1, 2 and 3 are the most common, with Types 1 and 3 suspected to be the foremost toxic isomers.[8] Grayanotoxins bind to the Group II receptor site on voltage-gated sodium channels.[9] The Na^+ channel then remains activated, resulting in prolonged depolarization and ensuing stimulation of the nervous system. This mechanism can lead to bradycardia, but it is unclear if it is caused by direct or indirect effects on cardiac myocytes. While intracerebral injections of GTX into albino rats caused bradycardia and respiratory depression suggesting the importance of their effects on the central nervous system, bilateral vagotomized rats injected with GTX did not develop bradycardia implying peripheral vagal stimulation in GTX-induced bradycardia.[10]

Several hours after ingestion, GTX causes nausea, vomiting, sweating and dizziness. Patients also may develop arrhythmias, from sinus bradycardia to third degree heart block. Altered sensorium is also a common finding. Blurry vision and hypersalivation may occur. Our patient exhibited gastrointestinal symptoms, waxing and waning mental status, and bradycardia treated with atropine.

Yilmaz, et al., described a case series of 66 patients who demonstrated dizziness, weakness, blurred vision, nausea, vomiting, syncope and salivation.[11] A heart rate less than 60 bpm was found in 87% of patients. A smaller case study showed the most common symptoms being hypotension in 100% of patients and bradycardia in 95%.[12] Interestingly, altered levels of consciousness caused by GTX toxicity has been described as early as 401 BC when Greek soldiers who had eaten honey acted drunk or crazy.[13]

Management of GTX poisoning is supportive until toxicity wanes. While there are case reports of atrial fibrillation,[14] bradydysrhythmias are the most common cardiac manifestations of GTX toxicity that may be corrected with atropine.[15] Kim, et al., described three cases of patients suffering from GTX toxicity from ingestion of Rhodendron species who developed conduction disturbances and bradycardia treated successfully with atropine.[16] A similar case of a 21-month old child who ingested a *Pieris japonica* plant was found to have similar signs and symptoms of vomiting and bradycardia with improvement after atropine administration.[17]

Intralipid emulsion therapy (ILE) is a proposed therapy for GTX poisoning. The most widely accepted hypothesis for the mechanism of action of ILE is that it acts as a lipid sponge that binds and extracts lipophilic poisons from tissues. This has been studied in *Andromeda* species ingestion in goats that experienced clinical improvement.[8] No case of treatment with ILE has been described in humans to date.

Our patient was successfully extubated on the first hospital day without complication. Her vital signs returned to normal, and she was discharged later that day in normal state of health. The Japanese pieris (*Pieris japonica*), commonly known as the Andromeda plant, was identified by the family. It is a broadleaf evergreen shrub commonly found in the Northeastern United States, where it grows wildly and is also found cultivated in gardens. During a PubMed search using key words "pieris," "Andromeda," "Grayanotoxin," crossed by keywords "toxicity" and "poisoning," we found there has only been one other documented case of human ingestion of Pieris japonica, which was mentioned above.[17]

Grayanotoxin poisoning is rare and can cause life-threatening toxicity with gastrointestinal signs, altered levels of consciousness, and bradycardia with absence of QRS prolongation and hyperkalemia. Treatment is supportive with administration of atropine for symptomatic bradycardia. Consultation with a medical toxicologist is advised in all cases.

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