Peer Reviewed Case Report

Idiopathic Phenobarbital-Responsive Hypersialosis: An Unusual Form of Limbic Epilepsy

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Presentation and Day 1
Molly, a 7-year-old, 57-lb, spayed Labrador retriever, presented to the Matthew J. Ryan University of Pennsylvania Veterinary Hospital with a 6-week history of vomiting and severe hypersalivation. During these 6 weeks, Molly was seen by her local veterinarian several times: abdominal radiography did not reveal a gastric or intestinal foreign body, and treatment with antiemetics was unsuccessful.

On presentation at the University of Pennsylvania, Molly was quiet, alert, responsive, and hypersalivating. Her heart rate was 95 bpm, which is within normal limits (i.e., 70 to 150 bpm) for a dog her size. Molly’s respiratory rate was 28 breaths/min, which is within normal limits (i.e., 16 to 30 breaths/min). All other physical examination results, including temperature (101.1°F), were within normal limits.

The differential diagnosis for regurgitation or vomiting and hypersalivation includes megaesophagus, esophagitis, mechanical obstruction (e.g., gastrointestinal [GI] foreign body), hiatal hernia, myasthenia gravis, botulism, tetanus, immune-mediated disease, hypoadrenocorticism, idiopathic hypersalivation, and infectious disease.1 Tetanus and botulism were ruled out because of the duration of clinical signs. Both of these infections would have progressed to life-threatening complications by 14 days after clinical signs appeared.

Thoracic radiographs were obtained to check for cervical and thoracic abnormalities that could cause vomiting (or regurgitation) and hypersalivation. The results were normal for a dog of Molly’s age, ruling out megaesophagus.

During Molly’s first morning at the hospital, she regurgitated twice but seemed comfortable. Later that afternoon, Molly’s status changed: her temperature was 103.3°F; her heart rate was 132 bpm; her blood pressure was 136/72 (normal: 110/55 to 190/110 mm Hg), with a mean arterial pressure of 96 mm Hg (normal: 75 to 90 mm Hg); and she appeared uncomfortable. An arterial catheter had not been placed, and no treatments had been initiated. Her respiratory rate and effort increased, and she began producing a lot of upper airway noise that was not heard on presentation. Molly then began to exhibit abnormal behaviors. She scrunched her head and neck toward her body, hypersalivated even more, and made a reverse sneeze-like noise, after which she regurgitated a moderate amount of clear, foamy fluid.

After this, Molly seemed to be normal. Once she had calmed down, blood was taken and submitted for an acetylcholine receptor antibody titer to rule out myasthenia gravis, which has three clinical presentations: focal, generalized, and acute fulminating.2 All of these presentations can include pharyngeal and laryngeal dysfunction, megaesophagus, regurgitation (with or without aspiration pneumonia), excessive salivation, dysphagia, coughing, retching, weakness, and respiratory failure.3 Because Molly presented with some of these signs, we had to rule out myasthenia
Molly was fasted throughout the first day because of the regurgitation episode and to prepare for anesthesia the next morning. During the evening, Molly was offered a small amount of water every 6 hours. The rest of the afternoon and the evening were uneventful.

Day 2
On day 2 of hospitalization, an 18-gauge IV catheter was placed, through which Molly began receiving 118 mL/h of Normosol-R (Abbott Laboratories). Molly was sedated with 0.05 µg/kg of buprenorphine and 0.3 mg of midazolam IV, and anesthesia was induced with 8 mL of propofol given to effect until she could be intubated. Anesthesia was maintained with isoflurane at 2% to 2.5%. Then Molly was prepared for a laryngeal examination, retroflex rhinoscopy, and an upper-GI endoscopic examination. These procedures did not detect any abnormalities (e.g., masses, foreign bodies). Molly’s larynx appeared normal and was functioning properly. Biopsies were taken during the rhinoscopy and the GI endoscopic examination (duodenum and stomach samples); the results would be available in a few days.

Molly began receiving metoclopramide hydrochloride (1 mg/kg/d constant-rate infusion), ranitidine (2 mg/kg IV q12h), and ampicillin (22 mg/kg IV q8h). During the rest of the day, Molly continued to hypersalivate, with only one episode of “reverse sneezing” followed by regurgitation. It was determined that Molly was regurgitating, rather than vomiting, because she did not retch to bring up fluid. During the regurgitation episode, Molly was very uncomfortable but was aware of her surroundings. The rest of Molly’s day was uneventful.

Day 3
Molly’s condition started to deteriorate. She had several regurgitation episodes that included reverse sneezing, breath holding, severe hypersalivation, and abnormal neck contraction, followed by regurgitation.

During the midafternoon, Molly had acute respiratory distress after regurgitating, was depressed, had a respiratory rate of 54 breaths/min, and had cyanotic mucous membranes. Flow-by oxygen was immediately administered. An electrocardiogram showed sinus tachycardia with a heart rate of 220 bpm (normal: 70 to 150 bpm). Molly was receiving oxygen when the arterial blood was obtained for analysis. The results of an arterial blood gas analysis were as follows:

- \( P_{aO_2} \): 116 mm Hg while receiving flow-by oxygen (normal: 91 to 118 mm Hg)
- Carbon dioxide: 15 mm Hg (normal: 30 to 40 mm Hg)
- \( HCO_3^- \): 13 mmol/L (normal: 18 to 24 mmol/L)
- Base excess: 9 mmol/L (normal: \(-2 \pm 2 \) mmol/L)
- pH: 7.54 (normal: 7.35 to 7.45)

These results are indicative of metabolic alkalosis with a low arterial oxygenation level despite administration of 40% to 50% flow-by oxygen, indicating that Molly needed additional oxygen supplementation. Molly’s \( P_{aO_2} \) should have been 190 to 238 mm Hg at sea level, based on the following equation:

\[
50\% \text{ (oxygen inspired)} + 21\% \text{ (room air)} = 2.38\% \text{ (i.e., } P_{aO_2} = 238 \text{ mm Hg)}
\]

(An intubated patient receiving 50% oxygen should have a \( P_{aO_2} \) of 238 mm Hg if its lungs are normal.)

Because Molly’s \( P_{aO_2} \) was low and the doctor suspected that she had aspirated during her latest regurgitation episode, she was placed in an oxygen cage in the intensive care unit (ICU). Thoracic radiographs were not obtained because Molly was deemed too unstable to be removed from the oxygen cage.

In the oxygen cage, Molly continued to receive Normosol-R (120 mL/h) and metoclopramide (1 mg/kg/d CRI). She was given butorphanol (0.2 mg/kg IV q4–6h as needed) for discomfort. Ticarcillin with clavulanic acid (50 mg/kg IV q6h), which is a broad-spectrum antibiotic, was initiated for possible aspiration pneumonia.

Molly had a good evening in the oxygen cage. An overnight arterial blood gas analysis was performed after she had been breathing room air for approximately 20 minutes. The results were as follows:
• PaO₂: 73 mm Hg (normal: 91 to 118 mm Hg)
• Carbon dioxide: 40.5 mm Hg (normal: 30 to 40 mm Hg)
• HCO₃⁻: 26 mmol/L (normal: 18 to 24 mmol/L)
• Base excess: 1 mmol/L (normal: −2 ± 2 mmol/L)
• pH: 7.419 (normal: 7.35 to 7.45)

These results showed that Molly’s metabolic alkalosis had improved greatly. Molly was also oxygenating better when not receiving oxygen supplementation.

**Day 4**

Molly remained in the ICU and continued having episodes of neck scrunching, reverse sneezing, regurgitation, and hypersalivation. Except for these episodes, her physical parameters remained steady (i.e., blood pressure: 161/69; mean arterial pressure: 89 mm Hg; heart rate: 100 bpm; pulse oximetry reading: 92% on room air). When Molly’s electrolytes were checked, her potassium level was a little low (3.4 mg/dL [normal: 3.5 to 5 mg/dL]). The metoclopramide dosage was increased to 2 mg/kg/d CRI, and 7 mEq of potassium chloride was added to 250 mL of Normosol-R. Molly still appeared to be uncomfortable while receiving butorphanol, so it was changed to buprenorphine (0.01 mg/kg IV q4–6h as needed for pain).

A CBC, blood chemistry panel, and resting cortisol level were obtained. Molly’s resting cortisol level was low (2.0 µg/dL [normal: 5.5 to 20 µg/dL]), so the adrenocorticotropic hormone (ACTH) stimulation test was completed to rule out atypical Addison’s disease. Patients with Addison’s disease can present with vague, waxing and waning clinical signs, possibly including regurgitation, decreased appetite, lethargy, electrolyte abnormalities, and weight loss. Molly’s electrolyte levels were within normal limits, but if she had had typical Addison’s disease, she would have been hyperkalemic and hyponatremic. Although Molly did not have the classic electrolyte abnormalities associated with Addison’s disease, a diagnosis of atypical Addison’s disease was still possible because her clinical signs were waxing and waning and she was regurgitating. The CBC and chemistry panel results were within normal limits and the ACTH stimulation test result was 21.6 µg/dL (normal: 5.5 to 20 µg/dL), which ruled out atypical Addison’s disease. Molly’s cortisol level might have been elevated due to stress and her disease process. Therefore, a second ACTH stimulation test was planned for a future date.

The acetylcholine receptor antibody titer result was 0.32 mmol/L (normal: <0.6 mmol/L), which ruled out myasthenia gravis. The biopsy samples from the rhinoscopy and the upper GI endoscopic examination consisted of normal tissue.

**Day 5**

Molly was still experiencing episodes (10 to 15 per day) of hypersalivation, reverse sneezing, and regurgitation. She continued to receive the following medications: metoclopramide hydrochloride (2 mg/kg/d CRI), ranitidine (2 mg/kg IV q12h), ticarcillin–clavulanic acid (50 mg/kg IV q6h), and buprenorphine (0.01 mg/kg IV q6h as needed for pain).

Although Molly had not been diagnosed with idiopathic phenobarbital-responsive hypersialosis (hypersalivation), the clinician decided to treat Molly for it because she had some similar clinical signs (see Discussion) and was not responding to traditional treatments for these clinical signs. Molly began receiving phenobarbital (2 mg/kg IV), and within 4 hours after the first dose, she appeared more comfortable. The hypersalivation decreased over the course of the day.

**Day 6**

Molly continued to improve and appeared very comfortable. Buprenorphine was discontinued, and metoclopramide was decreased to 1 mg/kg/d. Molly continued to receive ticarcillin and ranitidine as initially prescribed. She was offered small amounts of a bland diet and slowly began eating.

**Day 8**

After 3 days of receiving phenobarbital, Molly was no longer hypersalivating or experiencing episodes of reverse sneezing, neck contraction, and regurgitation. Because she was doing very well, metoclopramide and ranitidine were discontinued. Molly continued to eat a bland diet, and her medications were converted to oral formulations. Ticarcillin–clavulanic acid was discontinued, and amoxicillin–clavulanate potassium (375 mg q12h) was initiated. Oral phenobarbital was initiated at 2.5 mg/kg q12h.

**Discharge From the Hospital**

Molly continued to receive phenobarbital and to improve.
On day 10, she was discharged from the hospital. She continued to receive phenobarbital (2.5 mg/kg PO q12h), amoxicillin–clavulanate potassium (375 mg PO q12h), and a bland diet.

**Follow-Ups**

At a 10-day recheck, Molly was still doing very well and had not had any episodes since she was in the hospital. Molly had four rechecks within 6 months and has been doing extremely well. We have started to taper her off of phenobarbital and are hoping that she will not have a relapse.

**Nursing Management**

Molly’s regurgitation and constant hypersalivation were difficult to manage because they required constant cleaning of the bedding and rewrapping of the IV catheter. Molly’s bed had to be changed several times a day, even when it was covered with absorbent plastic-bottomed covers. We routinely rewrap IV catheters every day, but Molly’s catheter often became soiled or wet from hypersalivation, requiring it to be rewrapped many times a day to prevent infection.

We monitored Molly’s vital signs every 4 to 6 hours to detect subtle changes as well as dehydration due to large water loss resulting from regurgitation and hypersalivation. An extended database consisting of blood gas analysis results, a packed red blood cell count, and a total solids level was obtained every 8 hours to monitor Molly’s electrolyte values and hydration status.

Nutrition is an extremely important part of any sick animal’s recovery. Because Molly was regurgitating often, she was not offered oral feedings. A central catheter could have been placed in her saphenous vein to provide intravenous nutrition, but Molly’s owners declined this because of financial concerns. Placement of a central catheter in the jugular vein was contraindicated because of Molly’s abnormal neck movements during her regurgitation episodes. Molly was fasted until day 6, when she stopped regurgitating. For the remainder of her hospitalization, Molly enjoyed several small, bland meals throughout each day, and she did not vomit or regurgitate.

Because this case was unusual and Molly’s medical status changed quickly during hospitalization, 24-hour care and monitoring was required to detail each abnormal episode in the medical record and notify the lead clinician. Molly’s episodes were not treated with medication, but the technicians comforted Molly during the episodes.

This rare case taught the doctor and technicians a great deal. I do not think Molly will be forgotten. She continues to do well at home 1 year after being hospitalized.

**Discussion**

Idiopathic phenobarbital-responsive hypersialosis is an uncommon syndrome that has been reported in humans and dogs. Common signs include hypersalivation, vomiting and/or regurgitation, and swollen, painful salivary glands.3 Molly also experienced episodes of reverse sneezing and abnormal neck contraction. This syndrome is presumed to be a form of limbic epilepsy—a type of epilepsy in which seizure activity originates from the limbic system.

The limbic system is a system of structures common to the brains of all mammals.6 This system is associated with olfaction, emotion, motivation, behavior, and various autonomic functions.6 The limbic system plays a major role in controlling somatic and visceral motor behavior.7 Signs of limbic epilepsy include hypersalivation, vomiting, and pupillary dilation.8

Schroeder and Berry5 conducted a retrospective study on 19 dogs that presented with similar clinical signs (e.g., enlarged salivary glands, retching, vomiting, regurgitation) but had different diagnoses. Of the 19 dogs, phenobarbital (2 mg/kg q12h) was administered to seven dogs, four of which markedly improved.7 In three of the cases, phenobarbital was administered for at least 2 weeks and then tapered and discontinued. One dog could not be weaned off of the drug, so it continued the treatment for 2 years.7

Boydell et al9 conducted a study on 13 dogs with retching, gulping, weight loss, reluctance to exercise, snorting, lip smacking, nasal discharge, drooling, reduced food consumption, and depression. After an in-depth workup, phenobarbital was administered to rule out phenobarbital-responsive sialadenosis. Within 24 to 36 hours after drug administration began, 11 of the 13 dogs improved; 1 week after drug administration began, clinical signs in these 11 dogs had completely resolved.8 In one case, owner compliance was poor, and the dog was euthanized at the owner’s request. The other clients complied with the treatment because they quickly learned that stopping it caused the clinical signs to reappear.9

**References**


5. Schroeder H, Berry WL. Salivary gland necrosis in dogs: a retro-

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*Phenobarbione is a formulation of phenobarbital that is unavailable in the United States.*