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Case Report

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Central diabetes insipidus following cardiopulmonary arrest in a dog

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Abstract

Objective – To describe a clinical case of transient central diabetes insipidus (CDI) occurring post cardiopulmonary arrest (CPA) in a dog.
Case Summary – An 8-week-old dog presented for intensive care after successful resuscitation following CPA. The patient exhibited neurologic deficits at initial presentation and over the following days developed marked polyuria, isosthenuria, and low urine osmolality. Treatment with synthetic vasopressin resulted in a reduction in urine output, increase in urine specific gravity (>50%), and increase in urine osmolality, suggesting a diagnosis of partial CDI. Clinical signs resolved over the following weeks and treatment was discontinued.
New or Unique Information Provided – CPA has been described as a cause of ischemic injury to the pituitary gland resulting in CDI in people. To the authors' knowledge, this is the first report of a dog developing transient partial CDI following CPA and successful resuscitation.

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Keywords: cardiopulmonary resuscitation, complications, neurological injury

Abbreviations

ADH	antidiuretic hormone
CDI	central diabetes insipidus
CPA	cardiopulmonary arrest
CRI	continuous rate infusion
GCS	Glasgow coma scale
MGCS	modified Glasgow coma scale
TBI	traumatic brain injury
USG	urine specific gravity

Introduction

Central diabetes insipidus (CDI) refers to a polyuric syndrome characterized by a partial or complete lack of production of vasopressin, or antidiuretic hormone (ADH), from the neurohypophysis.[1] Clinical signs include increased thirst and excessive urine output. Laboratory abnormalities include hyposthenuria or isosthenuria, low urine osmolality, increased serum sodium concentration, and normal or increased serum osmolality.[1] Posterior pituitary dysfunction and ADH deficiency leading to CDI has been described in the human literature secondary to traumatic and ischemic brain injury.[2–12] In these reports, development of CDI carries a guarded prognosis, especially in pediatric patients. Causes of CDI in veterinary patients include inflammation, pituitary malformation, neoplasia, cysts, and idiopathic causes. In addition, there are reports of CDI associated with traumatic brain injury (TBI) in dogs and cats. [1,13–20] In this report, we describe a case of transient partial CDI in an 8-week-old dog that likely incurred ischemic brain injury post cardiopulmonary arrest (CPA) and successful resuscitation.

Case Summary

An 8-week-old male intact Golden Retriever was referred for intensive care post CPA. The dog was initially evaluated by the primary care veterinarian for vomiting and diarrhea. Radiographs were suspicious for a gastric foreign body and the patient was anesthetized for endoscopy, which progressed to exploratory laparotomy. During anesthesia, the patient suffered a CPA. Return of spontaneous circulation was achieved with external chest compressions, IV epinephrine[a] (0.06 mg/kg IV), atropine[b] (0.01 and 0.03 mg/kg IV), and manual ventilation with 100% oxygen. The estimated time of CPA was

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2–3 minutes. The patient remained intubated for 3 hours. During this time he was hypotensive and systolic blood pressure was not readable with Doppler.[c] A biochemistry panel revealed hypoproteinemia (39 g/L [3.9 g/dL]; reference interval, 54–82 g/L [5.4–8.2 g/dL]) and hypoalbuminemia (23 g/L [2.3 g/dL]; reference interval, 25–44 g/L [2.5–4.4 g/dL]). A complete blood count revealed a hematocrit (HCT) of 0.29 L/L [29.5%] (reference interval, 0.32–0.5 L/L [32%–50%], and was otherwise within normal limits. The patient was administered IV crystalloids (10 mL/kg),[d] IV colloids (14 mL/kg),[e] and IV fresh frozen plasma[f] (12.5 mL/kg) over approximately 6 hours. The patient was extubated but remained hypotensive with neurologic signs including paddling of limbs, opisthotonus, and a stuporous mentation. A diazepam[g] bolus was administered (0.3 mg/kg IV) and the patient was transferred to our facility for ongoing treatment.

At presentation the dog was laterally recumbent, exhibited opisthotonus, and was intermittently paddling with all 4 limbs. Menace was absent bilaterally. Pupils were mid-range and nonresponsive to light and he was vocalizing. Gag reflex was present. He was assessed as having a Modified Glasgow Coma Scale (MGCS) of 12. Body weight was 4.0 kg. Temperature was 37.0°C (98.6°F), and heart rate was 220/min. The patient had pink mucous membranes and normal lung sounds bilaterally. The patient remained spontaneously breathing with adequate ventilation, as evidenced by normal partial pressure of carbon dioxide in the venous blood. Urine specific gravity (USG) was 1.020. Electrolytes were within reference interval, including sodium (144.1 mmol/L [144.1 mEq/L]; reference interval, 144–156 mmol/L [144–156 mEq/L]). Blood glucose was 6.7 mmol/L (122 mg/dL) (reference interval, 6.6–25 mmol/L [119–450 mg/dL]). Systolic blood pressure was not readable with Doppler[c] and a cursory echocardiogram revealed an underfilled left ventricle. The patient was administered a total of 150 mL/kg IV fluids[d] over the following 8 hours. The patient remained hypotensive (systolic pressure 60 mm Hg) and developed mild peripheral edema and increased body weight (4.76 kg). He was started on a norepinephrine[h] continuous rate infusion (CRI) (0.1 μg/kg/min IV), and blood pressure normalized (ie, systolic pressure measured >90 mm Hg) over the following 6 hours. The patient was considered euvolemic but overhydrated at this point based on adequate filling of the left ventricle, normal heart rate and plasma lactate concentration, and the increase in body weight over 10%. A 0.5 mg/kg dose of furosemide[i] was administered IV. Recheck albumin was 12 g/L (1.2 g/dL) and the patient was administered 25% human albumin[j] via CRI (3.5 g/kg over 24 hours). Serum sodium at this time was 138.4 mmol/L (138.4 mEq/L), and crystalloid fluid therapy[k] was adjusted to 2 mL/kg/h. A urinary catheter was placed to allow urine quantification.

Due to continued neurologic signs a diazepam[g] CRI was initiated (0.5 mg/kg/h IV) and a fentanyl[l] CRI (4 μg/kg/h IV) was added for postoperative analgesia. The patient remained intermittently vocal and anxious. Incremental propofol[m] boluses were given, totaling 25 mg (6 mg/kg) IV. The patient's head and neck were elevated 30 degrees, and flow-by oxygen was provided at 4 L/min. Twelve hours after presentation the patient was stuporous with minimal response to noxious stimuli and was intermittently vocalizing. He was laterally recumbent with tetraparesis, opisthotonus, and intermittent paddling. Sedative drugs were temporarily withheld and a neurologic examination was performed. Assessment was compatible with a severe diffuse brain lesion, considered secondary to a diffuse hypoxic event to the brain. A 6.2% hypertonic saline[n] (3 mL/kg IV) bolus was administered over 20 minutes due to the patient's deteriorating neurologic status. Sodium at this time was 142.8 mmol/L (142.8 mEq/L). Recheck albumin following the 25% human albumin[j] transfusion was 25 g/L (2.5 g/dL). Due to ineffective sedation, the diazepam[g] was discontinued, and intermittent low doses of dexmedetomidine[o] (0.5 μg/kg IV) were administered. A dexmedetomidine° CRI was then initiated at 1 μg/kg/h IV.

An abdominal ultrasound performed on day 2 revealed hyperechoic fat in the right cranial abdomen suspicious for pancreatitis, and severely reduced gastrointestinal motility. The patient was initiated on a metoclopromide[p] CRI (1 mg/kg/day IV), and administered maropitant[q] (1 mg/kg SC) and esomeprazole[r] (0.7 mg/kg IV). A nasogastric tube was placed and residual fluid was aspirated intermittently; this was used to provide enteral nutrition on day 4. The dexmedetomidine° CRI was discontinued the morning of day 3 and the patient was maintained on intermittent methadone[s] boluses (0.3 mg/kg IV) for continued postoperative analgesia and sedation. He was rousable, responded to stimuli, and the opisthotonic episodes were less frequent. Thoracic auscultation at this time revealed crackles in the right hemithorax, and thoracic radiographs showed an alveolar pattern suspicious for aspiration pneumonia. An endotracheal wash was not performed due to the patients diminished neurologic status, and broad spectrum antimicrobials were initiated (ampicillin[t] 22 mg/kg IV every 8 hours and enrofloxacin[u] 10 mg/kg IV every 24 hours). Oxygen saturation remained over 96% with flow-by oxygen at 2 L/min.

The patient developed polyuria (urine output 9 mL/kg/h) on day 3, with a USG of 1.012 and no change in body weight. He was maintained on IV crystalloids[v]

at 6 mL/kg/h and IV colloids[e] at 1 mL/kg/h. He was offered water every few hours during periods of alertness and appeared to be subjectively polydipsic, although quantification of water intake was not recorded. Electrolytes were monitored every 6 hours, and sodium ranged from 142.8 to 144.0 mmol/L (142.8–144.0 mEq/L). On day 4, the methadone[s] boluses were discontinued and buprenorphine[w] (0.015 mg/kg IV) was administered every 6–8 hours. The patient remained polyuric (urine output 12 mL/kg/h) and isosthenuric (USG 1.012). Serum sodium increased to 148.2 mmol/L (148.2 mEq/L). Care was taken to match IV fluid rate with urine output; the IV crystalloid[v] rate was increased to 9 mL/kg/h with concurrent colloid[e] administration at 1 mL/kg/h.

On day 5, urine output remained high (10 mL/kg/h). Crystalloid fluids[v] were reduced to 8 mL/kg/h, colloids[e] were reduced to 0.5 mL/kg/h, and isosthenuria persisted (USG 1.012). Urine osmolality was low at 249 mOsm/L (reference interval 500–1,200 mOsm/L), increasing suspicion for the presence of CDI. Desmopressin[x] (DDAVP) was administered (1 drop in the conjunctiva every 12 hours), and within 24 hours USG increased to 1.032 (>50%). Serum sodium at this time was 143.5 mmol/L (143.5 mEq/L), and reduced to 140 mmol/L (140 mEq/L) 6 hours later. Urine output was decreasing on day 6 at 4 mL/kg/h, and IV crystalloids[v] were reduced accordingly. Colloids[e] remained at 0.5 mL/kg/h until being discontinued the following day. Hydration remained adequate with no significant change to serum sodium. Repeat thoracic radiographs revealed a resolving alveolar pattern. The patient was oxygenating well on room air; therefore, oxygen supplementation was discontinued. Crystalloid fluids[v] were reduced according to urine output. The patient was able to eat at this point and oral antimicrobials were initiated.

Complete neurologic assessment over day 3 and 4 had been impaired by the administration of sedative drugs, and serial MGCS were not performed; however, neurologic examination over days 5, 6, and 7 revealed improving mentation and motor function. MGCS at the time of discharge was 16. The patient was discharged on day 8; he was not able to ambulate but was attempting to move all limbs with support and had developed a marked intention tremor. The patient was discharged with subconjunctival desmopressin[x] (1 drop into 1 eye every 12 hours), amoxicillin-clavulanate[y] (13.75 mg/kg orally every 12 hours), metoclopramide[z] (5 mg orally 24 hours), and subcutaneous fluids[aa] (100 mL every 12 hours). At a recheck appointment 3 days later the patient was ambulatory with support. Urine osmolality was 370 mOsm/L. Desmopressin[x] and subcutaneous fluids[aa] were discontinued by the owner after 1 week and recheck 4 weeks after the initial event revealed urine osmolality of 647 mOsm/L. The patient had improved mentation, was ambulatory without support although ataxic, and had a remaining mild intention tremor.

Discussion

CDI refers to a polyuric syndrome resulting from lack of sufficient ADH to concentrate urine for water conservation. Complete deficiency causes severe diuresis and hyposthenuria (USG <1.006). Dogs and cats with partial CDI can concentrate their urine to an isosthenuric range (1.008–1.015) with restricted access to water, but cannot concentrate their urine over 1.015–1.020, even in the face of severe dehydration.[1] Nephrogenic DI (NDI) refers to an insensitivity of the V2 receptors to ADH at the level of the kidney, and can be acquired or congenital. Congenital NDI involves malformation of the V2 receptors, while acquired NDI results from other disorders that interfere with the normal interaction between ADH and the V2 receptors.[1] ADH is synthesized in the hypothalamus and released by the posterior pituitary gland in response to increased plasma osmolality, decreased arterial blood pressure, and reductions in circulating volume. It acts on V1, V2, and V3 receptors. Activation of V2 receptors causes insertion of aquaporin-2 channels in the luminal wall of the collecting ducts in the kidney and subsequent water reabsorption. Exogenous ADH in the form of synthetic vasopressin (DDAVP) is used to treat CDI and preferentially acts on V2 receptors in the same way.

The modified water deprivation test is the optimal diagnostic test to differentiate between CDI, primary nephrogenic DI, and primary (psychogenic) polydipsia.[1] This may not be accurate, however, in cases of partial DI. It can be challenging to perform, and bears with it the risk of worsening neurologic symptoms in a patient with existing neurologic impairment. Another accepted method of diagnosis is measurement of urine concentrating ability followed by evaluation of response to trial therapy with desmopressin (DDAVP).[1] An increase in urine concentration (>50%) provides strong evidence for CDI.[1] Urine osmolality is typically low in all 3 DI syndromes, although administration of DDAVP should cause an increase in urine osmolality in cases of CDI, as opposed to nephrogenic DI.[1] In the patient described in this report, urine osmolality and USG increased within 24 hours of administering DDAVP (USG >50% increase), increasing suspicion for CDI.[1] Studies in people with TBI have also relied upon response to treatment with DDAVP as a means of diagnosis.[9,11] Computed tomography (CT) or magnetic resonance imaging (MRI) can be performed to evaluate any visible lesions in the pituitary gland. One study describes that the absence of a hyperintense

signal on sagittal T1-weighted MRI can be a nonspecific indicator of CDI.[8] Another study in people with TBI reports the presence of vascular insults in only 50% of patients with known pituitary dysfunction,[2] which contradicts the previous study's findings.

Patients with CDI can have varying degrees of hyposthenuria or isosthenuria depending on the severity of disease and their water intake. Pediatrics in addition have a reduced renal concentrating ability, causing them to have a lower USG than adults. The patient described in our report presented with a USG of 1.020. It is not possible to determine to what degree this patient's age affected his urine concentrating ability, as a USG prior to the incident was not available. This USG could also have been affected by a limited free water intake, as well as previously administered IV fluids, including hetastarch, which can artifactually increase USG.[21] ADH release can be affected by other factors, including hypovolemia. Our patient was considered euvolemic within 24 hours of admission to our hospital based on normalized volume parameters; however, the polyuria continued through day 5. While previous fluid overload may have contributed to increased urine output, we consider the urine output of this patient too excessive to be accounted for by fluid overload alone. A human classification for CDI describes the criteria to include UOP >4 mL/kg/h for at least 2 consecutive hours, hypernatremia (serum sodium >145 mmol/L), high serum osmolality (>300 mOsm/kg), and low urine osmolality (<300 mOsm/kg).[9] Fifteen percent of dogs with CDI have hypernatremia; however, electrolytes are frequently normal and 20% of dogs reportedly demonstrate low serum sodium.[1] This is due to the renin angiotensin aldosterone system maintaining electrolyte homeostasis despite a markedly increased urine output.[1] These values may not be representative of critically sick patients in a hospital environment; other factors such as IV fluid therapy can have a profound effect on electrolytes in a patient that is unable to regulate sodium and water. Without access to free water in the face of ongoing polyuria, such patients can become profoundly hypernatremic and require intervention in the form of hypotonic solutions. Our patient was drinking water, which likely compensated for a portion of the free water loss, and care was taken to select IV fluids based on close electrolyte monitoring. Fortunately, extreme changes to serum sodium in this patient were avoided.

Alpha-2 agonists are commonly used in the human ICU for sedation of mechanically ventilated patients, and dexmedetomidine has been reported to cause polyuria through suppression of vasopressin in a dose-dependent manner by blocking ADH release and action.[22] One human case report described an increase in urine output and serum sodium concentration after 4 hours in a patient undergoing 6 hours surgical procedure who was receiving dexmedetomidine at a dose of 0.5 μg/kg/h. Upon discontinuing the dexmedetomidine, urine output normalized once the patient was admitted to the ICU for recovery.[23] Another human case report described polyuria with dexmedetomidine doses over 1 μg/kg/h without changes in serum osmolality, serum sodium, or USG. This was attributed to the fact that this patient was receiving 0.45% NaCl with 5% dextrose at the time so it was presumed that hypotonic losses were matched.[22] In this report, all laboratory measures normalized within 24 hours of discontinuing dexmedetomidine. An experimental study of 36 anesthetized adult mixed breed dogs measured vasopressin concentrations and urine osmolality among other variables in subjects receiving different concentrations of dexmedetomidine (1 μg/kg/h and 2 μg/kg/h) in 0.9% NaCl.[24] They found that urine output increased and urine osmolality and vasopressin concentrations decreased in dogs receiving dexmedetomidine, although measurements were not taken after discontinuing treatment. None of these reports involved patients with brain injury or evidence of ischemic damage to the pituitary gland. Although an important consideration, the polyuria associated with dexmedetomidine in the majority of these patients resolved within 24 hours. Therefore, we conclude that dexmedetomidine was not the cause of our patient's symptoms as his polyuria, low urine osmolality, and isosthenuria were still present 48 hours after discontinuing dexmedetomidine, and improved upon treatment with exogenous vasopressin.

CDI in dogs and cats has been uncommonly reported. Documented causes include neoplasia, pituitary cysts, and inflammatory conditions, and there have been several case reports of CDI post TBI in dogs and cats.[1,13–20] Foley et al described a complex of hypothalamic-pituitary deficiency secondary to TBI in a 12-week-old Great Dane puppy.[13] That patient had documented hypoadrenocorticism, hypothyroidism, and growth hormone deficiency in addition to CDI. A CT scan confirmed a fracture and hematoma at the level of the pituitary gland. Two case reports[17,18] describe cats that developed clinical signs of polyuria and polydipsia in the weeks to months following trauma that were subsequently diagnosed with CDI. Both patients were well enough at that time to undergo a water deprivation test. Platt et al described a case of secondary hypoadrenocorticism in a dog following trauma.[19] This report stated that damage to the hypothalamus, pituitary stalk, or pituitary gland could arise in association with direct trauma, shearing injury of the pituitary stalk, pituitary infarction, interruption of blood supply, fractures of the basal skull bones, and posttraumatic obstructive hydrocephalus. In our patient the suspected etiology was interruption of

blood supply during CPA, and possibly some degree of reduced perfusion during hypovolemia post CPA. This correlates with studies in people that describe CDI as a consequence of hypoxic-ischemic damage to the central nervous system from a variety of conditions including CPA.[8,11,12]

Endocrine dysfunction including CDI post TBI has been widely described in people.[2–7,9–12] In one study, the incidence of vasopressin deficiency post TBI was reported to be 3%–37%, and evidence of hemorrhage or ischemia in the hypothalamic-pituitary axis at postmortem examination was common.[2] Bondanelli et al describe that GCS was significantly lower in patients with pituitary dysfunction post TBI.[3] There is a limited amount of data available in veterinary medicine regarding the utility of the MGCS as a prognostic indicator. One veterinary study correlates an MGCS <8 with a worse outcome in patients with TBI.[25] There is less information available about how trends in MGCS affect prognosis, and there are no current veterinary publications associating MGCS with prognosis in cases of CDI. A human study evaluating 50 adult patients with moderate to severe brain injury revealed an incidence of CDI in 26%,[6] and another human study of 436 adults found CDI in 14.7% of patients with isolated head injury.[10] In this study, CDI was associated with more severe brain injury; independent risk factors for CDI included a GCS less than 8 and the presence of cerebral edema. The presence of CDI was an independent risk factor for death. This contradicts the previous findings of Agha et al showing that the presence of CDI post TBI was unrelated to the severity of head trauma as assessed by the GCS.[6] Earlier development of CDI in people has been associated with a worse prognosis. The development of CDI within the first 2 weeks of any neurologic insult has been associated with higher mortality rates in both adults and children (69%–85%), with the highest CDI-associated mortality rates seen in patients with TBI.[9] Yang et al reported a mortality of 77.8% at 2 months in children with CDI associated with acute brain insult, which was defined as any severe central nervous system injury including infection, hypoxic-ischemic events and cerebral hypoperfusion (including cardiac arrest, respiratory failure, carbon monoxide poisoning, and hypoxic encephalopathy), head injury, and vascular lesions. They stated CDI was a sign of severe brain damage in children and development of CDI within the first 2 days was a significant predictor of outcome.[11] Alharfi et al evaluated 180 children with severe TBI and found CDI in 18% of patients. The overall mortality rate in this patient population was 87.5%, with a 100% mortality rate seen in patients developing CDI within the first 2 days. The presence of cerebral edema was associated with mortality and the authors postulated cerebral edema could also induce CDI by increasing pressure on the pituitary gland.[9]

In veterinary medicine, the availability of humane euthanasia coupled with an uncertain or guarded prognosis infers that those patients with more severe brain injury may be more likely to be euthanized. In addition, the need for care at a 24-hour facility for these patients has financial implications that may prevent owners from proceeding with treatment. Therefore, CDI as a consequence of severe TBI or hypoxic-ischemic events may be underrecognized. Further diagnostics should be considered in a patient that is recovering from CPA with a sudden onset of polyuria, including serum electrolytes, USG, urine, and plasma osmolality. In addition, further endocrine testing should be considered in patients showing evidence of CDI in these scenarios due to the incidence of other concurrent endocrine abnormalities reported in the literature. While some studies report persistent CDI,[4,5,7] there is evidence to suggest this condition may be transient in people and animals.[4–7,14] Resolution has been reported to occur within a few weeks of injury in some species, which appears to have been the case with our patient.

Footnotes

[a] Epinephrine, IMS Limited, CA.
[b] Atropine sulfate, MED-PHARMEX Inc, CA.
[c] Ultrasonographic Doppler flow detector model 811-B, Parks Medical Electronics, OR.
[d] Plasmaltye A, Abbott Laboratories, North Chicago, IL.
[e] Hetastarch 6% in 0.9% NaCl, B. Braun Inc, CA.
[f] Fresh frozen plasma, Indyvet Emergency and Specialty Hospital, IN.
[g] Diazepam, Hospira Inc, Lake Forest, IL.
[h] Norepinephrine, Claris, North Bushwick, NJ.
[i] Furosemide, Intervet Inc, DE.
[j] Human serum Albumin 25% AlbuRx 25, CSL Behring LLC, IL.
[k] 0.9% NaCl, Abbott Laboratories.
[l] Fentanyl, WEST-WARD Eatontown, NJ.
[m] Propofol, Abbott Laboratories.
[n] Hypertonic saline 7.2%, Phoenix Clipper Distributing Company LLC, MO.
[o] Dexmedetomidine, Orion Pharma Pfizer Inc, NY.
[p] Metoclopromide, Hospira Inc, F.
[q] Maropitant, Pfizer Inc.
[r] Esomeprazole, Astrazeneca LP, Wilmington, DE.
[s] Methadone hydrochloride, Mylan Institutional LLC, IL.
[t] Ampicillin, Auromedics LLC, NJ.
[u] Enrofloxacin, Bayer Healthcare LLC, KS.
[v] Normosol R, Hospira.
[w] Buprenorphine, Stokes Pharmacy, NJ.
[x] Desmopressin 0.01%, Stokes Pharmacy.
[y] Clavamox, Pfizer Inc.
[z] Metoclopromide, Watson Pharma, Inc, India.
[aa] Lactated Ringers, Abbott Laboratories.

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