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Transient Fanconi syndrome with severe polyuria and polydipsia in a 4-year old Shih Tzu fed chicken jerky treats

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Summary

Acquired Fanconi syndrome is characterized by inappropriate urinary loss of amino acids, bicarbonate, electrolytes, and water. It has recently been described in dogs fed chicken jerky treats from China, a new differential diagnosis to the classical inciting infectious diseases (e.g. leptospirosis, pyelonephritis) and toxins. A dog fed exclusively chicken jerky treats purchased in Switzerland was presented to our clinic with severe polyuria, polydipsia and profound electrolyte and acid base disturbances. Other inciting causes of Fanconi syndrome were ruled out. The requirement of a very intensive supportive treatment in this dog stands in contrast to treatment of chronic forms of Fanconi syndrome as described in the Basenji. This intensive therapy and the associated monitoring can be a real challenge and a limiting factor for the prognosis of acquired Fanconi syndrome. Veterinarians should be aware of the risk of excessive feeding of chicken jerky treats.

Keywords: Fanconi syndrome, polyuria, renal tubulopathy, electrolyte disturbances, glucosuria

Vorübergehendes Fanconi Syndrom mit schwerwiegender Polyurie und Polydipsie bei einem 4-jährigen Shi Tzu nach Verfütterung von Hühnertrockenfleisch

Erworbenes Fanconi Syndrom ist charakterisiert durch pathologischen Verlust von Aminosäuren, Bikarbonat, Elektrolyten und Wasser über die Nieren. In den letzten Jahren wurden mehrere Hunde mit dieser Erkrankung in Zusammenhang mit Verfütterung von Hühnertrockenfleisch Belohnungen aus China beschrieben. Ein 4-jähriger Shi Tzu, ausschliesslich mit in der Schweiz gekauftem Hühnertrockenfleisch ernährt, wurde uns mit hochgradiger Polyurie, Polydipsie und schweren Veränderungen des Säure-Basen- und Elektrolythaushaltes vorgestellt. Andere Ursachen von Fanconi Syndrom wurden ausgeschlossen. Im Gegensatz zur beim Basenji beschriebenen Form benötigte der Hund eine sehr intensive Therapie und Überwachung, was eine Herausforderung und ein limitierender Faktor für die Prognose sein kann. Tierärzte sollten sich des Risikos einer übermässigen Fütterung von Hühnertrockenfleisch bewusst sein.

Schlüsselwörter: Fanconi Syndrom, Polyurie, renale Tubulopathie, Elektrolytveränderungen, Glukosurie

Introduction

Fanconi syndrome is a reabsorptive defect of the proximal renal tubules, which can result in loss of important solutes (Di Bartola 2006). The syndrome is well described as an inherited disease affecting Basenjis, but the acquired form has only been occasionally reported in veterinary medicine in association with various drugs including gentamicin, amoxicillin, and streptozotocin, and toxins such as lead and mercury (Roberts et al., 1982; Hostutler et al., 2004). Additionally, it has been described in a dog with primary hypoparathyroidism (Freeman et al., 1994), in dogs with copper hepatopathy (Appleman et al., 2008; Hill et al., 2008), in a dog with suspected pyelonephritis (Jamieson and Chandler, 2001), and in association with multiple myeloma and other dysproteinemias (Lacy et al., 1999). Proximal tubular dysfunction including some of the features of Fanconi syndrome have been further reported in dogs with acute kidney injury such as leptospirosis (Mastrorilli et al., 2008). A case published in 2011 (Hooper and Roberts, 2011) described acquired Fanconi syndrome in 4 dogs exposed to chicken jerky treats in the United States. In the period from 2006 to 2012, the U.S. Food and Drug Administration received many complaints that such treats made in China apparently were making dogs sick (FDA press release, 2012). Samples were tested negative for known causes of food-associated nephropathies such as drugs, toxins, heavy metals, and melamine. So far, no explanation could be found and the products were therefore not banned from the market. This report

describes a case of acquired, transient renal tubulopathy in a Shih Tzu fed excessively treats made from Chinese chicken purchased in Switzerland.

Case history

A 4-year old female spayed Shih Tzu (6.5 kg) was brought to the referring veterinarian with a history of acute vomiting, polyuria (PU), and polydipsia (PD) of 3 weeks duration. The dog had no previous illness and no known access to toxins. According to the owner, chicken jerky treats ("Swiss Dog", Delphin-Amazonia AG), were fed as the sole diet for the last several weeks before clinical signs started. Laboratory evaluation by the referring veterinarian had revealed a severe hyperchloremic metabolic acidosis, hyponatremia, hypokalemia, hypophosphatemia and a severe neutrophilia with left shift. Due to the lack of improvement to treatment with intravenous fluids, potassium chloride, sodium bicarbonate and marbofloxacin, the dog was referred for further diagnostics and management to the Small Animal Clinic of the University of Bern with a tentative diagnosis of Fanconi-like syndrome.

Physical examination and blood parameters

On referral, the dog presented lethargic, moderately dehydrated (7%), and with dull mentation. The physical examination was otherwise unremarkable. The CBC showed neutrophilia with a mild left shift (22.2×10^9/L segmented neutrophils (ref.: 3.0–11.5), 0.8×10^9/L bands (ref.: 0–0.3)). Relevant results of the plasma biochemistry panel are summarized in table 1. Basal aldosterone measurement[a] ([a]Dechra Specialist Laboratories, Cambridge, United Kingdom) showed a highly increased level (aldosterone 3739 pmol/l (ref.: 0–960)) reflecting strong activation of the RAAS system.

Urinalysis

Relevant results of urinanalysis are summarized in Table 1. Urine sediment did not show abnormalities and bacteriologic culture of the urine was sterile. Urinary protein electrophoresis showed a urinary loss of mainly tubular proteins and albumin (Fig. 1).

Tentative diagnosis

Based on these findings, a tentative diagnosis of proximal tubular injury was made, possibly in association with the consumption of chicken jerky treats, and further diagnostic evaluation was performed to rule out possible causes. Thoracic radiographs were within normal limits. Abdominal ultrasound revealed a hypoechoic pancreatic parenchyma surrounded by hyperechoic mesentery. The liver appeared slightly hyperechoic with a coarse echotexture.

Therapy

Upon admission to the intensive care unit, IV fluid therapy was initiated (Plasmalyte-A, Baxter SA) at 2 ml/kg/h supplemented with 80 mEq/L of potassium chloride). The dog received additionally oral supplementation of disodium hydrogenphosphate (Freka Clyss Klistier, Fresenius Kabi Schweiz AG) at a starting dose of 2.1 mmol q8h and sodium-bicarbonate at a starting dose of 300 mg/kg/d divided 3 times daily. Further treatments included antibiotics with marbofloxacin (Marbocyl FD, Vétoquinol, 3 mg/kg iv q24h) and antiemetics with maropitant (Cerenia, Pfizer, 1 mg/kg IV q24h), and metoclopramide (Paspertin, Abbott AG, 0.2 mg/kg iv q8h). Considering the hyposthenuria and the ongoing severe polydipsia despite aggressive IV fluid treatment, it was hypothesized that the severe PU was partly due to diabetes insipidus. A desmopressin treatment trial (Minirin Nasenspray, Ferring AG, one drop (1.5–4 ug) conjunctivally q12h) was initiated and discontinued after 5 days due to lack of improvement. A chlorothiazide diuretic (Esidrex 25, Novartis, 4.16 mg/kg po q8h) was additionally administered on day 4 with the hypothesis that a reduced fluid delivery to the distal nephron would increase proximal sodium reabsorption. Treatment resulted in progressively decreasing urine production after approximately 5 days. Therapy was monitored and adjusted based on daily assessment of venous acid-base status and serum electrolyte concentrations (Tab. 1). Acidemia persisted until day 7 of hospitalization, and hypokalemia until day 11 despite aggressive therapy.

To assure adequate nutrition and to facilitate weaning of IV fluid therapy an esophageal feeding tube was placed on the 4th day of hospitalization. Due to the development of hypoglycemia (2.1 mmol/L), glucose 5% was added to the IV fluids. To exclude liver dysfunction as the cause of hypoglycemia, blood ammonium level was assessed and found normal.

Follow-up and further therapeutic procedures

On day 7 of hospitalization the dog developed hemorrhagic diarrhea. Since hypoadrenocorticism could not be ruled out, especially in the face of persistent hyponatremia despite aggressive replacement, an ACTH-stimulation test was performed. Pending the results, IV fluids were changed to 0.9% NaCl and fludrocortison (Florinef, 0.01 mg/kg po q12h) was administered. The ACTH- stimulation test showed an adequate response (post ACTH cortisol 42 µg/dl (ref.: 6–17)), but, despite this result, serum sodium normalized within 24 hours of initiating mineralocorticoid therapy. For results of urinanalysis conducted the same day, see Tab. 1. CBC revealed a severe left shift with toxic neutrophils. Biochemical abnormalities included increased ALT (234 U/L, ref.: 26–126), increased AP (696 U/L, ref.: 9–132), increased AST (177 U/L, ref.: 22–76), and hypomagnesemia (Total-

Table 1: Relevant blood parameters and urinalysis before and during therapy. This table illustrates the difficulties to correct the hypokalemia and the hypophosphatemia, despite aggressive supplementation. Na, sodium; K, potassium; Cl, chloride; Phos, phosphate; HCO_3, bicarbonate; AG, anion gap; USG, urinary specific gravity; UPC, urinary protein creatinine ratio; Fe, fractional excretion; IV, intravenous; PO, peroral; BW, body weight.

		d-1	d1	d2	d3	d4	d5	d6	d7	d8	d9	d10	d22	Reference
Blood Parameters														
Na	mmol/L	148	133	139	138	136	128		137	133	143	147	150	142–154
K	mmol/L	2.2	2.8	3.2	3.0	3.3	3.2		2.6	2.0	2.9	3.3	4.8	4.2–5.3
Cl	mmol/L	123*	107	110	111	106	97		101	98	108	112	114	106–135
Phos	mmol/L		0.43	0.96	0.80	0.73	0.81		0.57	0.71	0.57	0.71	2.23	0.91–1.90
pH		6.93	7.25	7.14	7.18	7.26	7.33	7.31	7.37	7.37	7.38	7.42	7.38	7.32–7.52
HCO_3	mmol/L	8.0	9.0	12.4	11.4	15.5	13.8	16.9	20.6	19.3	22.7	21.4	26.4	18.4–26.8
AG	mmol/L	18	17.6	21.4	18.7	14.8	16.2		12.8	12.0	10.6	12.2	15.3	10.5–19.0
pCO_2	mmHg	37.9	21.2	30.5	37.8	26.1	49.9		36.3	34.4	38.8	33.8	45.7	24.9–46.9
Creatinine	µmol/L		34	33	25	26	29		19	19	16	16	47	52–117
Urea	mmol/L	5.5	4.3	5.5	5.7	5.6	7.5		4.3	3.3	2.1	1.8	4.4	3.3–10.8
USG			1.007			1.005			1.012					
pH			4.9			4.3			6.5					
Glucosuria			4+			4+			4+					negative
Ketonuria			2+			3+			1+					negative
UPC			3.5											0–0.2
FeK	%		47											< 20
FeNa	%		2											< 1
FeP	%		45											< 40
Treatment														
Total fluids	ml/kg/h		2.0	2.0	3.2	4.0	4.6	6.6	6.6	9.7	9.7	8.6	0	
K^+ IV	mEq/kg/d		3.8	3.8	3.8	3.8	3.8	7.7	7.7	13.5	13.5	11.5	0	
K^+ PO	mEq/kg/d		0	0.5	0.7	1.0	1.5	1.9	4.9	7.6	10.2	12.5	5	
Phos	mmol/kg/d		1.0	1.0	1.3	1.6	1.8	1.8	2.0	2.5	2.9	2.8	0	
$NaHCO_3$	mg/kg/d		300	300	462	492	492	484	394	407	672	275	0	
BW	kg		6.5	6.5	6.5	6.1	6.1	6.2	6.1	5.9	5.9	6.0	6.0	

* Reference range Cl (rDVM): 110–119 mmol/L

Mg 0.56 mmol/L, ref.: 0.63–0.96). Both potassium and phosphate were still markedly decreased (Tab. 1). Magnesium chloride was supplemented in form of an IV CRI at 0.08 mEq/h and metronidazol (15 mg/kg q12h iv) was added to expand the antibiotic regime and cover for anaerobs.

By day 10 of hospitalization, the dog's general condition had improved and the severity of the PU/PD had gradually decreased. The dog started to show appetite and an increased activity level. Intravenous fluids were reduced stepwise based on estimated urine output assessed by serial body weight measurements. Potassium and water supplementation were gradually transitioned from the IV route to the esophageal feeding tube.

On day 17, the dog became febrile (39.4 °C). A blood culture was submitted and revealed an infection with

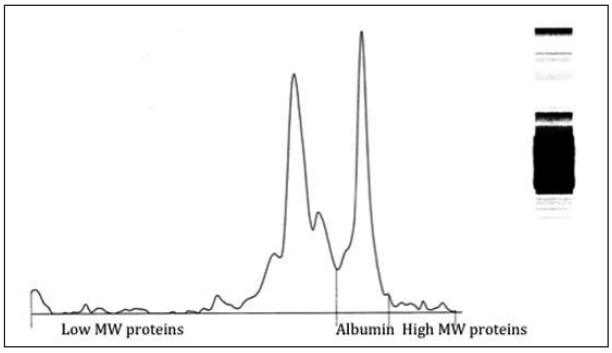

Figure 1: Urinary protein electrophoresis, demonstrating the urinary loss of low MW proteins (tubular proteins) and albumin. High MW proteins (glomerular proteins) were not detected in the urine, indicating a selective tubular injury. MW, molecular weight.

Acinetobacter spp.. Therapy was initiated with ampicillin-sulbactam (30 mg/kg iv q8h), according to the susceptibility testing, and the fever resolved within 2 days.

On day 23 of hospitalization the dog was discharged with the following medications and supplements: potassium chloride (1.7 mEq/kg po q8h), hydrochlorothiazide (4.2 mg/kg po q12h x14d), metoclopramide (0.5 mg/kg po q12h), marbofloxacin (3.3 mg/kg po q24h x14d), amoxicillin clavulanic acid (12.5 mg/kg po q12h x14d). Urinanalysis conducted the day before discharge revealed resolution of glucosuria, ketonuria, and proteinuria. Venous blood gas analysis confirmed resolution of acidemia.

The dog was re-examined by the referring veterinarian two days later. Serum potassium concentration was within normal limits and subsequently was reduced to twice daily administration. The previously prescribed marbofloxacin, metoclopramide, and hydrochlorothiazide were discontinued after 2 weeks of treatment. The dog was further evaluated at day 4, 1 week and 2 weeks after discharge. At the 3-week-evaluation, potassium supplementation could be stopped completely. The owners reported that the dog was doing well at home with no evidence of increased urination.

Discussion

Fanconi syndrome is a complex renal tubulopathy with marked proximal tubular dysfunction and loss of various combinations of amino acids, phosphate, glucose, bicarbonate, calcium, potassium, and other ions as well as potentially excessive urinary loss of water (DiBartola, 2006). The defective bicarbonate reabsorption leads to proximal renal tubular acidosis evidenced by acidic urine in the face of hyperchloremic metabolic acidosis. (DiBartola, 2006). The dog in this report demonstrated hyperchloremic metabolic acidosis, normoglycemic glucosuria, tubular proteinuria, and increased urinary fractional excretion of sodium, phosphate and potassium consistent with a generalized proximal tubular dysfunction. Urine amino acid profile to demonstrate additional amino acid reabsorption defect was not performed in this case due to the limited availability of this assay at the time.

Common clinical signs of Fanconi syndrome include ADH-resistant PU and PD, weight loss, weakness, and poor hair coat (Yearley et al., 2004). The dog in this report exhibited profound PU/PD, reaching up to 350 ml/kg/d when spontaneous water intake was included, and presented a real therapeutic challenge. Urine production and voluntary fluid intake by the dog (polydipsia) started to decrease gradually several days after initiation of the chlorothiazide (Lage, 1977; Takemura, 1998), and it is unclear if the normalization of the water homeostasis was due to the diuretic or progressive recovery of renal function.

The dog reported here, exhibited a marked hypoglycemia and glucosuria. Renal glucosuria is a very consistent finding in Fanconi syndrome patients but blood glucose concentration is typically within reference range (Bovee et al., 1982; Mainka, 1985; Guyton and Hall, 2011). Hypoglycemia is probably a result of profound urinary loss (Hooper and Roberts, 2011). Even though the dog developed sepsis later in the course of hospitalization, there were neither clinical nor clinicopathological signs of sepsis at the time of initial hypoglycemia. However, septicemia may have been present already before clinical signs were overt, especially considering the difficulties to maintain clean conditions in this markedly polyuric weak dog. Hypokalemia may be observed late in the course of disease (Easley and Breitschwerdt, 1976). It was however pronounced in the case reported here and this may represent the longstanding nature of the disease with depletion of intracellular stores as the dog displayed PU/PD for at least 3 weeks prior to presentation to a veterinarian. Hypokalemia likely contributed to the muscular weakness observed during the first days of hospitalization. A reduction in serum potassium may be further precipitated by alkali therapy, increasing the distal delivery of sodium and bicarbonate (DiBartola, 2006). Potassium citrate is therefore the preferred treatment in these dogs, addressing both alkalization and potassium supplementation. Correction of metabolic acidosis is difficult to achieve in proximal tubular acidosis because of the marked bicarbonaturia that develops when plasma bicarbonate concentration is increased to normal. The high sodium bicarbonate dosages used in this dog (up to 500 mg/kg/d) further support the diagnosis of proximal renal tubular acidosis.

Acquired causes of Fanconi syndrome are multifold (Yearley et al., 2004). In 2006, it was recognized for the first time in dogs consuming chicken jerky treats made in China (Hooper and Roberts, 2011). New reports of diseased dogs are still ongoing at the U.S. Food and Drug administration. Outbreaks have also been seen in Canada and Australia (Thompson et al., 2013). Up to date, no specific ingredient or contaminant has been identified and most affected dogs were toy to small breed dogs, suggesting a potential higher exposure of a putative toxin relative to their body weight. According to the owner, the dog received chicken jerky treats as a sole diet over a prolonged period. The manufacturer of the reported brand confirmed orally that the meat used for the treats was imported from China. Therefore, based on this report, veterinarians and owners should be aware of the potential risk of chicken jerky treats even when bought in Switzerland, similarly to treats bought in the USA (Hooper and Roberts, 2011).

Leptospirosis as a possible cause of acquired Fanconi syndrome was dismissed based on the lack of typical clinical signs and a negative canine IgM ELISA (Abdoel, 2011) for the detection of IgM directed against Leptospira spp that was conducted at the day of admission.

Urine culture was negative in the dog described in this report, not supporting pyelonephritis as a cause of renal glucosuria (Jamieson and Chandler, 2001). Other inflammatory diseases such as nephritis or pancreatitis may be considered as possible causes. The role of the echographic findings suggestive of pancreatitis is debatable. Canine PLI was unfortunately not submitted. However, the dog showed no clinical signs suggestive of acute pancreatitis, other than anorexia and neutrophilia with a left shift.

In acute Fanconi syndrome, the mainstay of treatment is aggressive supportive care managing fluid and electrolyte disturbances. If known, the causing factor should be eliminated. In our case, the treat was discontinued and the dog was supported intensively until renal tubular recovery was evident, approximately 17 days later. Medical management of both acute and chronic Fanconi syndrome is based on the Gonto protocol (Yearly et al., 2004). There are no studies comparing this protocol to other therapies. However, in one study (Yearly et al., 2004) median survival time for congenital Fanconi syndrome affected Basenjis treated with this protocol was 5.25 years. In our case, the Gonto protocol was modified to address the specifics of the profound metabolic disturbances associated with the acquired acute form of the Fanconi syndrome. With progressive recovery of renal tubular functions, the dog could be weaned off all medications and supplements and showed no evidence of residual damage or functional impairment.

Prognosis for acquired Fanconi syndrome is generally good if the trigger can be removed. However, as illustrated with this case – intensive support and management of fluid and electrolyte disorders can be very challenging. In a retrospective study of dogs with acquired Fanconi syndrome, 6 out of 102 (6 %) dogs died or were euthanized as a result of their illness, while survivors required ongoing treatment up to six months for resolution of clinical signs (Thompson et al., 2013). In many dogs with persistent, chronic Fanconi syndrome progressive renal dysfunction is the main concern and the most common cause of death or euthanasia.

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References

Abdoel T. H.: Rapid test for the serodiagnosis of acute canine leptospirosis. Vet. Microbiol. 2011, doi: 10.1016/j.vetmic.2011.01.015.

Applemann E. H., Cianciolo R., Mosenco A. S., Bounds A. E., Al-Ghazlat S.: Transient acquired Fanconi syndrome associated with copper storage hepatopathy in 3 dogs. J. Vet. Intern. Med. 2008, 22: 1038–1042.

Bovee K. C., Anderson T., Brown S., Goldschmidt M. H., Segal S.: Renal tubular defects of spontaneous Fanconi syndrome in dogs. In: Animal models of inherited metabolic diseases. Eds. R. J. Desnick, D. F. Patterson, Alan Liss Inc, New York, 1982, 435–444.

DiBartola S.: Fluid, electrolyte, and Acid-base disorders in small animal practice. Ed. S. DiBartola, Elsevier Saunders, 2006, 253–280.

Easley J. R. und Breitschwerdt E. B.: Glucosuria associated with renal tubular dysfunction in 3 Basenji dogs. J. Am. Vet. Med. Assoc. 1976, 168: 938.

Freeman L. M., Breidschwerdt E. B., Keene B. W., Hansen B.: Fanconi's syndrome in a dog with primary hypoparathyroidism. J. Vet. Intern. Med., 1994, 8: 349–359.

Hall J. E.: Diuretics, kidney diseases. In: Guyton and Hall, Textbook of Medical Physiology. Eds. A. C. Guyton and J. E. Hall, Saunders Elsevier, Philadelphia, 397–410.

Hill T. L., Breitschwerdt E. B., Cecere T., Vaden S.: Concurrent hepatic copper toxicosis and Fanconi's syndrome in a dog. J. Vet. Intern Med. 2008, 22: 219–222.

Hooper A. N. und Roberts B. K.: Fanconi syndrome in four Non-Basenji dogs exposed to chicken jerky treats. J. Am. Anim. Hosp. Assoc. 2011, 47: 178–187.

Jamieson P. M. and Chandler M. L.: Transient renal tubulopathy in a Labrador retriever. J. Small Anim. Pract. 2001, 42: 546–549.

Lacy M. Q. and Gertz M. A.: Acquired Fanconi syndrome associated with monoclonal gammopathies. Hematol. Oncol. Clin. North Am. 1999, 13:1273–1280.

Lage A. L.: Nephrogenic diabetes insipidus in a dog. J. Am. Vet. Med. Assoc. 1973, 163:251.

Mainka S. A.: Fanconi syndrome in a Basenji. Can. Vet. J. 1985, 26: 303–305.

Mastrorilli C., Dondi F., Agnoli C., Turba M. E., Vezzali E., Gentilini F.: Clinicopathologic Features and Outcome Predictoris of *Leptospira interrogans* Australis Serogroup Infection in Dogs: A retrospective Study of 20 Cases (2001–2004). J. Vet. Intern. Med. 2007, 21: 3–10.

Roberts M. C., Seawright A. A., Ng J. C., Normal P. D.: Some effects of chronic mercuric chloride intoxication on renal function in a horse. Vet Hum Toxicol 1982, 24: 415–20.

Takemura N.: Successful long-term treatment of congenital nephrogenic diabetes insipidus in a dog. J. Small Anim. Pract. 1998, 39: 592.

Thompson M. F., Kessel A. E., Steenhard L. A., Foster S. F.: Acquired proximal renal tubulopathy in dogs exposed to a common chicken treat: retrospective study of 108 cases (2001–2009). Aust. Vet. J. 2013, 91: 368–373.

Yearley J. H., Hancock D. D., Mealey K. L.: Survival time, lifespan, and quality of life in dogs with idiopathic Fanconi syndrome. J. Am. Vet. Med. Assoc. 2004, 225: 377–383.

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