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Transient renal Fanconi syndrome in a Chihuahua exposed to Chinese chicken jerky treats

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Summary

Transient Fanconi syndrome without azotemia was diagnosed in a dog and was associated with ingestion of Chinese chicken jerky treats. Fanconi syndrome is a proximal renal tubular defect and a diagnosis was made based upon severe glucosuria with normoglycemia, and severe generalized aminoaciduria. The clinical signs of polyuria and polydipsia as well as the massive urinary metabolic abnormalities resolved after jerky treat withdrawal. While frequently seen in North America and Australia, this is the first report of jerky treat induced Fanconi syndrome in continental Europe. Clinicians should be aware of this potential intoxication and be vigilant for a history of jerky treat consumption in a dog with glucosuria.

Keywords

aminoaciduria; nephrotoxin; glucosuria; metabolic disease; nutrition

Introduction

Fanconi syndrome (FS) describes a broad defect in the proximal renal tubules affecting the reabsorption of glucose, amino acids, phosphate, bicarbonate, sodium, potassium and water (10). The disease was initially described in dogs as an inherited syndrome in Basenjis, where it occurs as an autosomal recessively inherited trait, due to a homozygous mutation in the *FAN1* gene (4). Basenjis first show clinical signs between the ages of 4 and 7 years (18). An acquired FS resulting from exposure to antibiotics, like amoxicillin (3) and gentamycin (5), and in conjunction with copper storage hepatopathy (1, 13, 16) and primary hypoparathyroidism (9) has also been rarely reported in dogs. Since 2007, there have been numerous cases of acquired FS in dogs receiving chicken, duck or sweet potato jerky treats in North America and Australia (2, 8, 10, 14, 17). Only recently, in 2014, was one case of

jerky treat induced FS reported from the United Kingdom (6). Most of the treats contained products imported from China, but despite extensive investigations the causative toxin has not been found (8, 10). In many of these cases the FS has been transient, with glucosuria resolving within 1–8 months of treat withdrawal. However a number of dogs have developed acute or chronic renal failure and some have died (8, 17). We describe here the first reported case of transient FS in a small breed dog from continental Europe following the ingestion of Chinese chicken jerky treats.

Case Description

A 3-year-old spayed female Chihuahua was presented to the primary care clinic with a 2-week history of polydipsia and polyuria.

On presentation the dog appeared anxious but no abnormalities were detected upon physical examination. A non-starved blood sample was collected into lithium heparin and serum tubes. A free catch urine sample was obtained. Immediate examination of the urine in the clinic with a urine dipstick strip and of the lithium heparin whole blood sample with a handheld glucometer (Glucomer, Menarini, Austria) revealed severe glucosuria (1000 mg/dL) in the absence of hyperglycemia (94 mg/dL). The urine specific gravity (USG) measured with a refractometer was 1.020 and pH on the dipstick was 6.0. The serum sample was centrifuged after clotting, and the serum separated and used for subsequent clinical chemistry analyses. The blood and serum samples were sent to a reference laboratory (Labor Invitro, Vienna, Austria) where clinical chemistry and haematology analyses were performed 18–24 hours after collection on a Dimension ExL (Siemens, Austria) and an Advia 2120i (Siemens, Austria) respectively. The clinical chemistry results confirmed euglycemia in the serum sample (glucose 89 mg/dL, reference interval [RI] 65–120 mg/dL, hexokinase method). In addition, a mild hypoproteinemia (total protein 5.7 g/dL, RI 6.0–7.5) and hypoalbuminaemia (2.4 g/dL, RI 2.5–3.5), a moderate hypophosphatemia (0.7 mmol/L, RI 0.9–1.6 mmol/L) and hypocalcemia (2.03 mmol/L, RI 2.3–2.9 mmol/L) and two-fold increase in serum glutamate dehydrogenase (GLDH) activity above the RI (18.4 U/L, RI < 6.0 U/L) were found. Serum fructosamine concentration was within the RI (304 µmol/L, RI 203–377 µmol/L). There was no evidence of azotemia based on serum creatinine (0.6 mg/dL, RI 0–1.2) and urea (20 mg/dL, RI 20–54) concentrations (within the RI). A complete blood count revealed no abnormalities.

The dog had almost exclusively been fed treats containing chicken jerky. The owner had been feeding the treats for a few months together with small amounts of home-cooked food. Further examination of the treats revealed that they were produced in China and consisted of either strips of dried meat which contained 95% chicken according to the packaging label or of biscuits wrapped in meat strips, which were also of chicken origin (Figure 1). The owner reported that the dog only ate the meat strips and left the biscuits. There was no history of antibiotic or other drug administration or exposure to other described nephrotoxins apart from the jerky treats. A second dog in the household refused to eat the treats and was clinically healthy.

The owner was advised to stop feeding the dog with jerky treats and biscuits on day 3 and to return for a reevaluation in 5 days. On day 5 there was still severe glucosuria (> 1000 mg/dL Roche Cobas Combur 10 Test Roche Diagnostics Limited, Rotkreuz, Switzerland) as well as a mild proteinuria (sulfosalicylic acid test, opalescent but print still readable through tube) present. The urine sediment contained much cellular debris suggestive of inflammation; examination of the urine sediment was, however, limited by a high degree of cellular degeneration. Based on the urinalysis and previous blood results, an acquired FS was suspected.

A urine sample, collected by cystocentesis on day 11, revealed persistent severe glucosuria and mild proteinuria with a USG of 1.060. Only a few erythrocytes and leukocytes were present in the sediment. The owner reported an improvement in the degree of polyuria and polydipsia. On day 23 another urine sample still showed severe glucosuria. Analysis of urinary amino acids (Biocontrol, Bioscientia GmbH, Ingelheim, Germany) revealed a severe generalized aminoaciduria, with up to 100-fold elevations of urinary amino acids above the upper limit of the RI confirming the diagnosis of FS (Table 2). The most dramatic elevations were seen for glutamine, alanine, valine, lysine, glycine and leucine with increased excretion of virtually all other physiological amino acids.

No information regarding blood gases or acid-base status was available in this case as the equipment necessary for these point-of-care analyses was not available.

During follow-up examinations over the next 2 months the dog was clinically normal, but there was still persistent mild glucosuria (monitored by urine dipstick by the owner). Hypophosphatemia (0.5 mmol/L) was also still noted. Total protein, albumin and calcium concentrations and GLDH activity were within the reference interval. On day 70, repeat urinary amino acid analysis showed only slight residual increases in threonine, citrulline and lysine levels (Table 1, Figure 2). By 6 months following withdrawal of the jerky treats, the glucosuria had also resolved, and the dog was reported to be clinically healthy and readily eating a regular canine diet. This case was reported to the Austrian Bundesamt fuer Ernaehrungssicherheit.

Discussion

The initial presentation of a dog with glucosuria and concurrent normoglycemia was consistent with a FS, which was confirmed by demonstrating a severe generalized aminoaciduria (10). That the patient was a small breed dog with massive exposure to jerky treats originating from China and no other toxins raised the suspicion of an acquired FS caused by these treats. Although this problem had not been reported in Europe at the time of initial diagnosis, reports from North America and Australia since 2007 had raised the level of awareness and vigilance of the authors for this disease (8, 10, 17).

The Chihuahua is not a predisposed breed for inherited FS, but small breed dogs with a body mass under 10 kg are over-represented in reports describing jerky treat associated FS (11, 17). This is presumably because these breeds are more likely to be picky about their food

and therefore be offered these treats, and because of a higher treat to body weight ratio compared to larger breed dogs (17).

Dogs with FS associated with Chinese jerky treats rarely show severe clinical signs and in some cases the glucosuria may be an incidental finding (10). The most common clinical signs are polyuria and polydipsia, as in this case, due to osmotic diuresis and possible renal failure (10). Other unspecific signs like inappetance, vomiting, diarrhea and depressed habitus are also common (10). Weight loss and weakness also occur due to loss of amino acids. The disease may progress to chronic renal failure (17). As clinical signs are often non-specific, obtaining a comprehensive history is important. Owners should be questioned as to diet and supplements including pet jerky treats. If there is a history of an affected dog receiving pet jerky treats, further information regarding the composition and origin should also be obtained and reported to the country's official agency. Owners should be routinely cautioned that pet jerky treats are not an appropriate diet for dogs, hard to digest and may contain yet to be identified toxins. The dog in this report was almost exclusively fed Chinese chicken jerky treats.

A severe glucosuria in the absence of hyperglycemia and a generalized aminoaciduria are hallmarks of FS (4, 10). Other clinicopathological findings usually include increased urinary loss of phosphate, calcium and potassium (4). An impaired bicarbonate reabsorption leads to a metabolic acidosis (7). Hereditary isolated glucosuria, as reported in Norwegian Elkhounds, was also initially included here as a differential diagnosis. However, in this syndrome there is a defect only in the tubular transport of glucose and reabsorption of amino acids, calcium, phosphate and bicarbonate is normal (15). Severe generalized aminoaciduria occurs in FS due to decreased reabsorption of amino acids in the proximal renal tubules (4). Although the sample for amino acid analysis was taken 3 weeks after the treats had been withdrawn, massive glucosuria and aminoaciduria were still present, thereby confirming the diagnosis of FS. Fortunately, the glucosuria and aminoaciduria had nearly resolved 2 months after pet jerky treat withdrawal.

The hypophosphatemia and hypocalcemia are also consistent with increased loss of calcium and phosphorus through the kidney, caused by the FS (7). A measurement of urinary fractional electrolyte excretion would have been interesting here but was not carried out; increases in the fractional excretion of sodium, potassium and phosphorus have been reported with FS (6, 17). The initial hypoproteinemia and hypoalbuminemia are most likely a result of protein loss through the kidney.

The increase in serum GLDH activity in the absence of increased activity of other liver enzymes which was present at initial examination was not investigated further but had resolved 3 weeks after treat withdrawal. Eleven out of 21 Australian dogs with jerky treat associated FS had increased serum alanine aminotransferase (ALT) activity at initial examination, which persisted in 2 of 5 dogs for which follow-up information was available (8, 17). Hence, jerky treats, may result in hepatic as well as renal damage, although the mechanism is not known.

The mainstay of treatment is to remove the inciting jerky treats as soon as possible (10). Continued feeding can result in more severe and persistent FS or even fatal renal failure, while early immediate withdrawal limits the damage and the FS can be reversible (10, 11, 17). In this case the owner was advised to stop feeding the pet jerky treats after the initial diagnosis and the FS resolved within 2 months. Although in this case the FS resolved without specific therapy, severely affected dogs may require supportive treatment in order to correct the acid-base and electrolyte imbalances and other deficiencies (phosphorus, calcium, bicarbonate, amino acids, and vitamins) that are often present (12). Impaired bicarbonate reabsorption in the proximal renal tubule results in a variably hyperchloremic metabolic acidosis (7). Correction of this acidosis with parenteral or oral bicarbonate therapy is the most important treatment goal, according to a published protocol for the treatment of FS in Basenjis ((www.basenji.org/ClubDocs/fanconiprotocol2003.pdf) (12). Other treatment goals include normalizing electrolyte concentrations by providing potassium supplementation based on blood potassium values and giving oral phosphorus and calcium supplements, if a hypocalcemia or hypophosphatemia is present. Dogs with polyuria should be given a multivitamin supplement in order to replace trace minerals and vitamins lost via urine washout. A positive protein balance should be maintained by feeding a high-quality protein diet in order to offset the urinary amino acid losses. This should take the form of a high-quality dry food diet. In dogs with advanced renal insufficiency, a lower protein (renal) diet with amino acid supplementation may be advisable in order to slow down the progression of the renal disease (10, 12).

To the authors' knowledge this is the first case report of FS related to chicken jerky treat consumption in continental Europe. A similar case was reported in the United Kingdom in April 2014 (6). Until this year, all cases had occurred in North America or Australia. By the beginning of May 2014, the United States Food and Drug Administration (FDA), had received around 4800 complaints regarding disease in dogs (5600 animals with 1000 deaths), cats (24 animals) and 3 people reported to be potentially associated with the consumption of either chicken, duck or sweet potato jerky treats, most of which were imported from China (8). In around 60% of reported cases the disease involved the gastrointestinal tract with or without increased liver enzyme activity, in 30% the urinary tract including 220 cases of likely FS based upon glucosuria; in 10% of cases other organ systems like skin and nervous tissue were affected (8). However, many were later found to have other illnesses unrelated to jerky treat consumption. The FDA is currently investigating the disease spectrum and link between these reported cases, FS and jerky treats. In Australia, 108 cases of FS in dogs exposed to chicken breast treats from China were documented between September 2007 and June 2009 (17). A causative agent has not yet been identified and potential toxins that have so far been investigated by the FDA and others include *Salmonella*, heavy metals, irradiation markers, pesticides, antibiotics, antivirals, mycotoxins, rodenticides, known nephrotoxins (including melamine) and endotoxins. In this case, although no specific link was investigated or could be proven, the patient was receiving large quantities of chicken jerky treats made in China when the FS developed, and the disease resolved following withdrawal of the treats, similar to many of the cases described in North America and Australia. Why so few cases of FS related to jerky treats have occurred in Europe thus far is not clear. It is possible that the sources for jerky treat production in

Europe are different to those used for the North American market and that jerky treat producers in different areas use different manufacturing techniques. Toxicity suspected to occur as a result of jerky treat consumption should be reported to the relevant authorities (in Austria to the Bundesamt fuer Ernaehrungssicherheit, in Germany to the Bundesamt fuer Verbraucherschutz und Lebensmittelsicherheit).

Conclusions for practice

This case report provides important information regarding FS and its association with pet jerky treats originating in China. Veterinarians and national veterinary boards in Europe should be aware of the threat these treats might pose to animals - mostly small breed dogs. A FS should be considered early on in the diagnostic work-up of normoglycemic glucosuria and owners questioned closely about the patient's diet - if there is a history of consumption of these treats, they should be immediately withdrawn. In most cases, withdrawal of the treats leads to a resolution of the FS. More severely affected animals may require treatment targeted at resolving electrolyte, mineral, acid-base and amino acid losses. If untreated or in severe cases, the syndrome may progress to renal failure and death.

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Figure 1.
Photograph of chicken jerky treats consumed by a dog with transient Fanconi syndrome.

Figure 2.

Chromatogram of urinary amino acids obtained with a Model 30+ aminoacid analyser (Biochrom, Cambridge, UK). (A) Normal canine urine showing only two large peaks of urea (left) and ammonia (right). (B) Patient's urine on day 23 showing dramatic increases in virtually all amino acids consistent with renal FS.

Table 1

Quantitative urinary amino acid excretion in a Chihuahua after 23 and 70 days of chicken jerky treat exposure. Treats were withdrawn on Day 3 after initial presentation of the patient.

Amino Acid	Days after Initial Presentation		Reference Range*
	23	70	
Threonine	1814	664	48–265
Serine	1122	282	82–470
Glutamine	5376	561	110–701
Proline	2636	7	Not detected
Glycine	2650	119	46–862
Alanine	6733	306	83–366
Citrulline	407	236	<58
Valine	3898	24	<37
Isoleucine	1305	5	<67
Leucine	2008	18	<55
Tyrosine	799	11	<37
Phenylalanine	792	12	<39
Ornithine	1690	25	<99
Lysine	3230	294	23–79
Histidine	797	72	<122
Arginine	436	66	<59

* Values in $\mu\text{mol/g}$ creatinine measured in urine spot samples