Renal dysplasia in boxers and Finnish harriers

Puppies from two litters of dogs were found to have severe polyuria and polydipsia. Four of the dogs were investigated by means of clinical examination, haematological and biochemical analysis, and urinalysis. A modified water deprivation response test was also performed in two of the dogs. Renal changes on postmortem examination in three of the dogs were found to be consistent with renal dysplasia. A possible explanation for the finding of hyposthenuria and the extreme polyuria and polydipsia in association with renal dysplasia may be lack of response to antidiuretic hormone owing to anomalous maturation of the renal tubules. Six other puppies from the two litters of dogs did not show any clinical signs of polyuria and polydipsia, although postmortem examination in one of them also revealed renal dysplasia. The clinical features of renal dysplasia may therefore vary greatly between individuals.

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INTRODUCTION

Renal dysplasia may be defined as disorganised development of renal parenchyma that is due to abnormal differentiation. Generally, dysplastic tissue is characterised by the presence of structures that are inappropriate for the stage of development of the organism, or by the development of structures that are anomalous. Familial renal dysplasia is a common cause of renal failure in juvenile dogs and has been described in a number of breeds (Osborne and O'Brien 1983, Bovee 1986, Hoppe and others 1990, Kerlin and VanWinkle 1995, Lees 1996). The diagnosis is based on light microscopic findings of immature fetal glomeruli and primitive tubules in the kidneys of adolescent or adult animals. The most frequently observed compensatory changes are hypertrophy and hyperplasia of the glomerular tufts and tubules, and secondary changes include inflammatory lesions and fibrosis (Picut and Lewis 1987, Hoppe and others 1990).

A genetic study in the shih tzu breed suggests a simple recessive mode of inheritance for renal dysplasia (Hoppe and others 1990), but the cause and pathogenesis of the condition in dogs is unknown. However, advances in molecular biology techniques have allowed rapid progress towards the elucidation of the genetic basis for congenital kidney disorders. In mice, various models lacking *Bcl-2*, *Wnt-4* or *Pax-2* gene expression show dysplastic or cystic changes in their kidneys (Stark and others 1994, Sorenson and others 1996), and human dysplastic kidneys show inappropriate expression of *Bcl-2* and *Pax-2* (Winyard and others 1996). Winyard and coauthors propose that cyst formation and dysplasia occur when expression of these proteins is aberrant, that their findings support the view that dysplasia results from defects during early nephrogenesis, and that renal dysplasia is pathogenetically heterogeneous.

In Sweden, chronic renal failure due to renal dysplasia is an increasing problem in young dogs. Since 1974 up until the time of writing, the disease has been diagnosed by renal histopathology in 546 dogs in Sweden in 76 different breeds (A. Hoppe, unpublished observations). The most common clinical findings at first presentation have been moderate polyuria and polydipsia, depression, hypersthenuria or isosthenuria, varying degree of azotaemia and in some cases, urinary tract infection and vomiting. The age of onset of renal failure varies from eight weeks to 10 years, but it generally occurs at between four and 24 months of age.

Nephrogenic diabetes insipidus (NDI) is a polyuric disorder in which urine is not concentrated despite the production of normal or increased amounts of antidiuretic hormone (ADH). Primary NDI is a rare disorder resulting from a congenital defect involving the cellular response of the renal tubule to vasopressin (Hays and Levine 1976, Feldman and Nelson 1996). Affected animals are presented at a young age with severe polyuria and polydipsia. In reported cases, urine osmolality and specific gravity have been in the hyposthenuric range (urine osmolality <300 mOsm/kg, urine specific gravity <1·002 in

1·007). In these cases, urine specific gravity does not increase above the isosthenuric range during water deprivation, and affected animals show no further response to exogenous vasopressin administration.

Acquired (secondary) NDI includes a variety of renal and metabolic disorders (pyelonephritis, chronic renal failure, hypercalcaemia, hyperadrenocorticism, hypokalaemia, hyperthyroidism, hepatic failure and pyometra) in which the renal tubules lose the ability to respond adequately to ADH. These disorders resemble primary NDI, but are referred to as acquired or secondary because vasopressin, vasopressin sites and postreceptor mechanisms responsible for water absorption are present (Feldman and Nelson 1996).

Although hyposthenuria is rare in cases with advanced renal disease, it has been reported and is most likely to occur in situations in which the structure or function of the distal tubule and collecting duct are disproportionately affected by the disease process (Hays and Levine 1976).

The present report describes four puppies with hyposthenuria and severe polyuria and polydipsia. Renal dysplasia was diagnosed on necropsy in three of the cases.

CASE HISTORIES

Litter 1

Three male boxer pups (pups 1, 2 and 3) were presented to the Small Animal Clinic at the Swedish University of Agricultural Sciences, Uppsala, for investigation at three months of age. The dogs came from a litter of seven (six males and one female). Another male and the female of the same litter had died at the age of three weeks, and the postmortem examination had revealed bacterial pneumonia. Pups 1 and 2 had a history (together with a third littermate not brought in for investigation) of severe polyuria and polydipsia since the age of four weeks. According to the owner, these dogs each consumed about 1·5 litres of water per day. The third puppy (pup 3) presented to the clinic had normal water consumption. This pup was brought in since the owner wanted to investigate one puppy from the same litter which was not polyuric or polydipsic.

In accordance with the wishes of the owner, pup 2 was euthanased after the initial clinical examination and sent for postmortem examination. Pup 3 remained clinically normal until the age of four months, when it fell from a table and started to have seizures. This puppy was euthanased at six months due to recurrent seizures, lethargy and inappetence, and was sent for postmortem examination. In pup 1, the severe polyuria and polydipsia decreased at five months of age, and were mild for the next four months. However, the dog was euthanased at 10 months of age due to severe signs of dullness, vomiting, inapperence and weight loss. No post-mortem examination was performed.

Litter 2

One five-month-old male Finnish harrier (pup 4) from a litter of five (two females and three males) was presented with a history of severe polyuria and polydipsia since birth. According to the owner, two of the littermates showed the same symptoms of continuously drinking throughout the day, including drinking their own urine. After initial investigation this dog was sent home and lived for another two months, drinking about 4 litres of water per day, before being euthanased and sent for post-mortem examination.

Clinical investigations

Clinical examination of the four dogs revealed no abnormalities and, except for the pronounced polyuria and polydipsia in two of the boxers (pups 1 and 2), and in the Finnish harrier, the dogs appeared otherwise normal. Samples for urinalysis were obtained from each puppy and blood samples were taken for further haematological and biochemical analysis. In order to determine whether endogenous ADH was released in response to dehydration and whether the kidneys could respond to ADH, a modified water deprivation response test was performed in one of the polyuric boxers (pup 1) and in the Finnish harrier. To minimise the effects of severe medullary washout, water intake was gradually limited to about 90 ml/kg/day 48 hours before, and to about 60 ml/kg/day 24 hours before, the water deprivation test was commenced.

Before initiation of the water deprivation test, all food and water was withheld, the bladder of each dog was completely emptied, and exact bodyweight and urine specific gravity and serum creatinine were determined for each of the dogs. During the test, the dogs were weighed, hydration and central nervous system status was evaluated, serum creatinine was rechecked and urine samples were taken for measurement of specific gravity at two-hour intervals. After six (pup 4) and eight hours (pup 1), the water deprivation tests were terminated due to dehydration and loss of more than 5 per cent of bodyweight. At the end of the test, neither of the dogs showed any signs of illness and they were given small amounts of water (10 ml/kg bodyweight every 30 minutes for two hours, and thereafter 50 ml/kg bodyweight overnight) to drink.

The following day, the water deprivation test was continued. On this occasion, at the start, the dogs were each given 20 µg of desmopressin acetate (by one one-dose pipette (Minirin, 0·1 mg/ml; Ferring AB, Malmö, Sweden)) as conjunctival drops; otherwise, the procedure was the same as for the previous day. This time the test was stopped in both dogs after six hours because of dehydration. To visualise the kidneys, renal ultrasonography was performed in pup 1 and intravenous urography was carried out in pup 4.

Laboratory findings

Laboratory findings are summarised in Table 1. The haematological results showed low haemoglobin values in all dogs except for pup 4. The total and differential white blood cell (WBC) counts were unremarkable in all dogs. The initial biochemical results in pup 1 revealed mild

hypoproteinaemia, azotaemia, glycosuria, hypocalcaemia (probably due to low albumin) and hyperphosphataemia at three months of age. At 10 months of age, this dog was presented with severe signs of dullness, dehydration and pale mucous membranes. Blood biochemistry showed decreased haemoglobin and doubled creatinine values compared with the first investigation (Table 1). Fluid therapy was given to the dog for two days, but as it did not improve, euthanasia was recommended.

Pups 2 and 3 showed mild increases in blood urea and phosphorus, respectively (Table 1). Haematological and biochemical results in pup 4 revealed no abnormalities except for a mild increase in serum alkaline phosphatase, which was also found in the other dogs probably due to bone growth in these young animals.

Urinalysis in pups 1 (at three months), 2 and 4 (at three and five months, respectively) revealed hyposthenuria and a low U-creatinine/S-creatinine ratio (Table 2). Seven months later, at 10 months of age, pup 1 showed isosthenuria and a lowered U-creatinine/S-creatinine ratio, compared with values determined at the first investigation. Pup 3 did not show any signs of polyuria and polydipsia, and results from the urinalysis revealed a normal urine specific gravity and a high U-creatinine/S-creatinine ratio. Urinary sediment did not reveal any red, white or epithelial cells, crystals, casts or bacteria in any of the dogs (Table 2).

Results of the water deprivation test in pup 1 revealed a rise in urine specific gravity from 1·007 to 1·008 within eight hours. In pup 4, water deprivation resulted in an increase in urine specific gravity from 1·005 to 1·007 within six hours. The urine concentrating ability following desmopressin acetate administration showed an increase from 1·005 to 1·007 within the first two hours in pup 1. Over the next four hours, the urine specific gravity reached a plateau of 1·006 in the same dog. During the vasopressin test in pup 4, the urine specific gravity rose from 1·005 to 1·007 within four hours. Two hours later, when the test was ended, the specific gravity was back to 1·005.

Ultrasonographic examination of the kidneys of pup 1 showed an irregular surface, and the renal medulla was decreased in size compared with normal kidneys. Intravenous urography of pup 4 revealed normal renal size and normal excretion of contrast material.

Postmortem examination

Significant pathological lesions were confined principally to the kidneys. Macroscopically, the kidneys were smaller than normal in two of the three puppies examined at necropsy (pups 2 and 3); this reduction in size was most pronounced in pup 3 (approximately 50 per cent of normal). Besides the diminished size, the kidneys of pups 2 and 3 were lighter than normal with a finely granular to slightly nodular surface and firm consistency. On a cut surface, multiple white streaks were observed radiating from the cortex to the medulla. In pup 4, the kidneys appeared macroscopically normal apart from the occurrence of numerous small white nodules measuring 1 to 3 mm in diameter on the surface.

Microscopic examination revealed similar lesions in all three cases at necropsy

Table 1. Haematological and biochemical findings in an asymptomatic dog (pup 3) and three dogs (pups 1, 2 and 4) with severe polyuria and polydipsia

Parameter	Reference range*	Pup 1 (3 months)	Pup 1 (10 months)	Pup 2 (3 months)	Pup 3 (3 months)	Pup 4 (5 months)
Haemoglobin (g/litre)	120–190	89	83	112	112	177
WBC ($\times10^9$/litre)	6·5–18·1	6·3	15·0	5·9	8·9	7·0
Neutrophils ($\times10^9$/litre)	3·0–11·5	4·8	12·0	3·8	4·5	3·9
Eosinophils ($\times10^9$/litre)	0·1–1·3	<0·1	0·2	0·2	0·2	<0·1
Basophils ($\times10^9$/litre)	0–0·2	<0·1	<0·1	<0·1	0·1	<0·1
Lymphocytes ($\times10^9$/litre)	1·4–4·8	0·6	1·5	1·1	3·2	3·6
Monocytes ($\times10^9$/litre)	0·1–1·5	0·8	0·5	0·8	0·8	0·1
Urea (mmol/litre)	3·0–9·0	28·7	NR	18·2	5·6	5·3
Creatinine (µmol/litre)	40–130	205	412	122	57	70
Glucose (mmol/litre)	3·9–5·6	6·2	4·1	6·3	7·2	4·5
Alkaline phosphatase (ukat/litre†)	<2·1	3·2	3·0	3·4	3·2	4·6
Bile acids (µmol/litre)	<30	3·7	2·1	30·0	0·9	NR
Calcium (mmol/litre)	2·0–3·0	1·9	NR	3·1	2·7	2·6
Phosphorus (mmol/litre)	0·8–2·0	4·69	3·99	1·01	2·54	2·1
Sodium (mmol/litre)	147–159	149	NR	156	150	NR
Potassium (mmol/litre)	3·7–5·6	5·3	NR	5·4	4·9	4·8
Protein (g/litre)	63–82	62	77	68	64	NR
Albumin (g/litre)	28–37	24	NR	27	25	NR

* Adult values
† ukat/litre (SI unit): 1 kat=1 mol/second
WBC: White blood cells, NR: Not recorded

Table 2. Results of urinalysis in an asymptomatic dog (pup 3) and three dogs (pups 1, 2 and 4) with severe polyuria and polydipsia

Parameter	Reference range*	Pup 1 (3 months)	Pup 1 (10 months)	Pup 2 (3 months)	Pup 3 (3 months)	Pup 4 (5 months)
Specific gravity	1·020–1·045	1·007	1·012	1·005	1·045	1·036
Glucose	neg.	neg.	neg.	neg.	neg.	neg.
Protein*	0	0	0	0	1	1
pH	6–7	6	7	7	7	7
U-creatinine/S-creatinine	>30	13·8	6·8	20·9	296	51

* Values represent semiquantitative evaluation based on a scale of 0 to 3

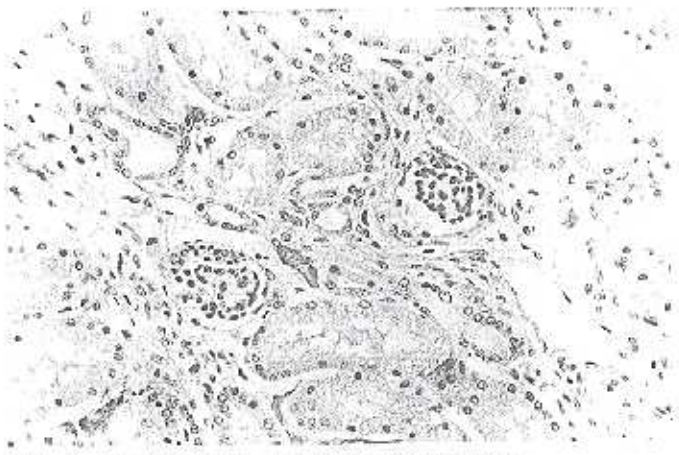

FIG 1. Pup 2. Renal cortex with fetal, immature glomeruli

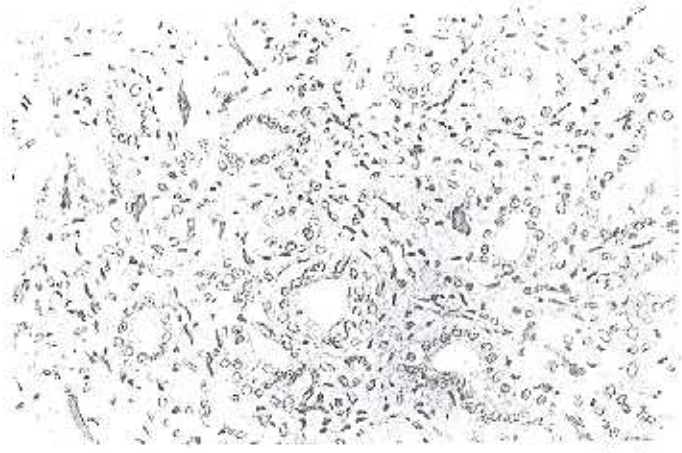

FIG 2. Pup 2. Renal medullary region showing dysplastic tubules lined by cuboidal/cylindrical epithelium and surrounded by loose mesenchymal tissue

The pathological findings were severe in pups 2 and 3, and mild in pup 4. In the cortex, fetal, immature glomeruli and foci with small, dysplastic tubular structures surrounded by immature mesenchymal tissue were observed (Fig 1). There were also hypertrophied glomeruli. In the medullary region, severely dysplastic, winding tubular structures lined by cuboidal to cylindrical epithelial cells were present (Fig 2). The dysplastic tubules were scattered in a loose mesenchyme. In pup 4, a heavy infiltration of predominantly mononuclear inflammatory cells was present in the pelvic region. No significant amounts of inflammatory cells were observed in the kidneys of pups 2 and 3.

In pup 3, a moderate degree of left ventricular hypertrophy was evident and the parathyroid glands were enlarged. There was also slight, microscopically detectable mineralisation of the interalveolar septa of the lungs. In pups 2 and 4, no non-renal pathological lesions were detected.

DISCUSSION

In this study, extreme polyuria and polydipsia was found in three puppies from two litters of dogs. Owing to the lack of response to the water deprivation test and the vasopressin response test, primary polydipsia and central diabetes insipidus were ruled out in pups 1 and 4. In pups 2 and 4, the severe tubular dysplastic lesions (particularly in pup 2) may explain the lack of response to ADH and concomitant hyposthenuria seen in such cases. Hyposthenuria due to renal disease was also indicated in pup 1 by the abnormal ultrasonographic findings of the kidneys, together with elevated serum urea, creatinine and phosphorus values. As this puppy grew older, a decrease in water intake and a change from hyposthenuria to isosthenuria was observed, which might reflect a progression in damage to nephrons and renal insufficiency. Unfortunately, no postmortem examination was performed on this puppy, but it may be speculated that the early signs of hyposthenuria in this dog, as well as in its littermate (pup 2), might be a consequence of a lack of response to ADH by the dysplastic renal tubules.

The symptoms of dog 3 were obscure. It never showed any clinical signs of polyuria and polydipsia and, at the age of six months, it was euthanased due to recurrent seizures. The aetiology of the seizures was never identified. One explanation could be trauma experienced as a result of the pup's fall from a table two months previously. However, at necropsy, the central nervous system was morphologically normal. Another explanation could be renal failure, since the macro- and microscopical lesions of the kidneys were pronounced, and seizures due to uraemia can occur.

Renal dysplasia in humans may be associated with a variety of organ malformations (Picau and Lewis 1987, Edward and Guillery 1997). These malformations are presumed to be a heterogeneous collection of disorders and their pathophysiology is enigmatic. Vascular disruption during early development may explain some of the cases associated with urological abnormalities, although these cases may also be associated with genetic defects (Devriendt and Fryns 1995). In the experience of the current authors, renal dysplasia in dogs may also be associated with multiple organ malformations, such as ectopic ureters, renal aplasia and renal hypoplasia.

Renal dysplasia has been described together with congenital Fanconi syndrome in two border terriers (Darrigrand-Haag and others 1996). Reports of Fanconi syndrome in dogs commonly describe adult dogs as having no other recognised renal disease. In the present report, lesions characteristic of renal dysplasia, with fetal glomeruli and segmental incomplete maturation of the nephrons, were described. It was not determined in the cases described by Darrigrand-Haag and others (1996) whether the renal tubular disorder leading to impaired reabsorption of amino acids, glucose, phosphorus

and bicarbonate was a consequence of renal dysplasia. However, dogs with renal dysplasia are characterised by having different percentages of immature nephrons, which persist throughout life, and the clinical signs manifested by each animal may be correlated with the segmental distribution of the disease, and with the part of the tubules which is most severely affected.

Conclusions

It can be concluded from the cases in the present report, as well as from those in other reports of renal dysplasia, that this developmental defect is a heterogeneous disorder. Individuals may initially show completely different clinical presentations before more typical signs of renal failure become evident.

References

Bovee, K. C. (1986) Renal dysplasia and renal tubular syndrome in the dog. In: Proceedings of the Fourth American College of Veterinary Internal Medicine Forum, Washington, DC, pp 13, 41-43

Darbishire-Hoag, R. A., Chew, D. S. A., Randolph, J. F., Lewis, R. M. & Webb, P. A. (1996) Congenital renal syndrome associated with renal dysplasia in 2 border terriers. *Journal of Veterinary Internal Medicine* 6, 417-419

Devriendt, K. & Proesmans, W. (1996) Genetic locus on chromosome 6p for multicystic renal dysplasia, pelvi-ureteral junction stenosis, and vesicoureteral reflux. *American Journal of Medicine and Genetics* 63, 385-387

Edwards, N. & Cuillen, M. D. (1997) Perinatal renal nephrology. *Current Opinion in Pediatrics* 9, 148-153

Feldman, E. C. & Nelson, R. W. (1996) Water metabolism and diabetes insipidus. In: Canine and Feline Endocrinology and Reproduction. Eds E. C. Feldman and R. W. Nelson. W. B. Saunders, Philadelphia, pp 9-37

Hays, R. M. & Levine, S. C. (1976) Pathophysiology of water metabolism. In: The Kidney. Eds B. M. Brenner and F. C. Rector. W. B. Saunders, Philadelphia, pp 675-676

Hoppe, A., Svensson, L., Jonsson, [illegible] & Hermanrud, A. (1990) Progressive nephropathy due to renal dysplasia in shih tzu dogs in Sweden: a clinical pathological and genetic study. *Journal of Small Animal Practice* 31, 83-91

Kerlin, R. L. & VanWinkle, T. J. (1995) Renal dysplasia in golden retrievers. *Veterinary Pathology* 32, 327-329

Lees, G. E. (1996) Congenital renal diseases. In: The Veterinary Clinics of North America, Small Animal Practice, Renal Dysfunction. Ed D. I. Polzin, W. B. Saunders, Philadelphia, pp 1379-1399

Osborne, C. A. & O'Brien, T. D. (1983) Renal dysplasia in Lhasa Apso and shih tzu dogs. In: Current Veterinary Therapy. 8th edn. Ed R. W. Kirk. W. B. Saunders, Philadelphia, pp 972-974

Picut, C. A. & Lewis, R. M. (1987) Microscopic features of canine renal dysplasia. *Veterinary Pathology* 24, 158-163

Sorenson, C. M., Padanilam, B. J. & Hammerman, M. R. (1996) Abnormal postpartum renal development and cystogenesis in the pcy/pcy mouse. *American Journal of Physiology* 271, F184-F189

Stark, K., Vainio, S., Vassileva, G. & McMahon, A. P. (1994) Epithelial transformation of metanephric mesenchyme in the developing kidney regulated by Wnt-4. *Nature* 372, 679-683

Weaver, F. J., Robson, R. A., Sava, D. R., Dressler, G. R. & Woo, A. F. (1995) The Pax2 transcription factor is expressed in cystic and hyperproliferative dysplastic epithelia in human kidney malformations. *Journal of Clinical Investigation* 98, 451-459