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 hypostenuria 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 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 puppies and has been described in a number of breeds (Osborne and O'Brien 1983, Bovee 1986, Hoppe and others 1990, Kohlin and Van Winkle 1995, Lee 1996). The diagnosis is based on light microscopic findings of immature renal glomeruli and primitive tubules in the kidneys of affected and normal 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 (Prince and Lewis 1987, Hoppe and others 1990).

A genetic study in the skin-tail 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 forsk-2 gene expression show dysplastic or cystic changes in their kidneys (Wang and others 1996, Svensson and others 1996), and human, dysplastic kidneys show inappropriate expression of Bcl-2 and Wnt-4 (Wang and others 1996). Watanabe and colleagues propose that eye formation and dysplasia occur when expression of these proteins is deficient, 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, hyperkalaemia, azotenaemia, 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 15 years, but it generally occurs between four and 24 months of age.

Nephrogenic diabetes insipidus (NDI) is a polycystic 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 responses of the renal tubule to vasopressin (Fager and Levine 1976, Feldman and Nelson 1980). Affected animals are presented in early age with severe polyuria and polydipsia. In reported cases, urine osmolality and specific gravity have been in the hyposthenuric range (Murphy et al. 1982).
1607). 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 (pyelectasia, chronic renal failure, hypercalcemia, hyperparathyroidism, hypokalemia, hyperphosphatemia, hypoalbuminemia, hypercholesterolemia, and pancreatitis) in which the renal tubules lose the ability to respond adequately to ADH. These disorders resemble primary NDI, but are related to its acquired or secondary because vasopressin, vasopressin receptors, and osmoreceptors are present in all species.

Although hypoosmolarity is rare in cases of advanced renal disease, it has been reported in young animals and is more likely to occur in situations in which the structure and function of the normal tubule are disrupted. Acquisitions of diabetes are disproportionately affected by the disease process.

The present report describes four puppies with hypoosmolarity and severe polyuria and polydipsia. Renal failure 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 in the Swedish University of Agricultural Sciences, Uppsala, for treatment 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 of loss (together with a third littermate not brought in for investigation) of severe polyuria and polydipsia since the age of four weeks. According to the owners, 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 puppy 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 owners, pup 1 was euthanized after the initial clinical examination and sent for postmortem examination. Pup 2 remained clinically normal until the age of four months, when it fell from a table and started to have seizures. This puppy was euthanized at six months due to recurrent seizures, edema, and inappetence, and was sent for postmortem examination. In pup 1, the severe polyuria and polydipsia decreased at five months, and were mild for the next four months. However, the dog was euthanized at 10 months of age due to severe signs of dehydration, vomiting, inappetence, and weight loss. No post-mortem examination was performed.

Litter 2
One five-month-old male Finnish boxer (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 the dog was sent home and lived for another two months, drinking about 4 litres of water per day, before being re-examined and sent for post-mortem examination.

Clinical investigations
Clinical examination of the four dogs revealed no abnormalities, except for the pronounced polyuria and polydipsia in two of the boxes (pups 1 and 2), and in the Finnish boxer, the dogs appeared otherwise normal. Samples for analysis 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 boxes (pup 1) and in the Finnish boxer. To minimize the effects of severe dehydration, water intake was gradually limited to about 30 ml/kg/day 54 hours before, and about 60 ml/kg/day 44 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, hydrated, and central nervous system status was evaluated, and urine samples were obtained and measured for measurement of specific gravity at room-temperature. After six (pup 4) and eight (pup 1), the water deprivation tests were terminated due to dehydration and loss of more than 5% of initial bodyweight. At the end of the test, the dogs showed signs of dehydration 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 29 μg of desmopressin (adenecin) to the nose and 1 ml of water (Minitol, 6:1 mg/ml; Vering AB, Malmö, Sweden) in a similar dose. 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 visualize the kidneys renal ultrasonography was performed in pup 1 and intravenous urography was carried out in pup 4.

Laboratory findings
Laboratory findings are summarized in Table 1. The haematological results showed low haematocrit values in all dogs except for pup 4. The total and differential white blood cell (WBC) counts were remarkable in all dogs. The initial biochemical results in pups 1 revealed mild
hypokatasthenia, anorexia, glycosuria, hypocalcaemia (probably due to low albumin) and hyperphosphataemia at three months of age. A 10 months of age, this dog was presenting with severe signs of dullness, dehydration and pale mucous membranes. Blood biochemistry showed decreased haematocrit 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.

Urine analysis in pups 1 (at three months), 2 and 4 (at three and five months, respectively) revealed hypokatalasthenia and a low U-creatinine/creatinine ratio (Table 2). Seven months later, at 10 months of age, pup 1 showed hypokatalasthenia and a lowered U-creatinine/creatinine ratio, compared with values determined at the first investigation. Pup 2 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/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, urine specific gravity resulted in an increase in urine specific gravity from 1-003 to 1-007 within six hours. The urine concentrating ability following desmopressin acetate administration showed an increase from 1-003 to 1-007 within the first two hours in pup 1. Over the next four hours, the urine specific gravity reached a plateau of 1-005 in the same dog. During the vasopressin test in pup 4, the urine specific gravity rose from 1-003 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 appearance of numerous small white nodules measuring 1 to 3 mm in diameter on the surface.

Microscopic examination revealed the lesions in all three cases as necropsy

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### 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference range*</th>
<th>Pup 1 (3 months)</th>
<th>Pup 1 (10 months)</th>
<th>Pup 2 (3 months)</th>
<th>Pup 3 (3 months)</th>
<th>Pup 4 (3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit</td>
<td>39-49</td>
<td>4.0</td>
<td>3.9</td>
<td>3.8</td>
<td>3.9</td>
<td>3.8</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>0.7-6.0</td>
<td>1.2</td>
<td>1.2</td>
<td>1.4</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>3.6-8.0</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>0.3-0.7</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.0-3.0</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Phosphorus (mmol/L)</td>
<td>0.8-1.6</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>137-147</td>
<td>142</td>
<td>142</td>
<td>142</td>
<td>142</td>
<td>142</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.7-5.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.0-9.0</td>
<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Alkaline Phosphatase (U/L)</td>
<td>2-10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference range*</th>
<th>Pup 1 (3 months)</th>
<th>Pup 1 (10 months)</th>
<th>Pup 2 (3 months)</th>
<th>Pup 3 (3 months)</th>
<th>Pup 4 (3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific gravity</td>
<td>1.003-1.010</td>
<td>1.007</td>
<td>1.007</td>
<td>1.007</td>
<td>1.007</td>
<td>1.007</td>
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<tr>
<td>Glucose (mg/dL)</td>
<td>0-175</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Protein*</td>
<td>0-1.5 mg/dL</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>pH</td>
<td>6.7-7.6</td>
<td>7.0</td>
<td>7.0</td>
<td>7.0</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>U-creatinine/creatinine</td>
<td>&gt;30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

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*Values represent the mean or median values from the samples of 1 to 3 dogs.
The pathological findings were severe in pups 2 and 3, and mild in pup 4. In the cortex, focal, immature glomeruli and focal with small, dysplastic tubular structures surrounded by immature mesenchymal tissue were observed (Fig 1). There were also hyperplastic 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 amount 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 interlobular septa of the lung. 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 osmopressin response test, primary polyuria 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 ADH1 and concentrated hypotonic urine seen in such cases. Hypotonic urine due to renal disease was also indicated in pup 1 by the abnormal ultrasonographic findings of the kidneys, together with the elevated serum urea, creatinine and phosphorus values. As this puppy grew older, a decrease in water intake and a change from hypotonic to isotononic urine 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 hypotonic urine 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 observed. It never showed any clinical signs of polyuria and polydipsia and, at the age of six months, it was euthanized due to recurrent seizures. The radiology of the skeleton was never identified. One explanation could be trauma experienced as a result of the polyuria fall in a rabbit two months previously. However, as recency of renal disease was morphologically normal. Another explanation could be renal fibrosis, since the macro- and microscopical lesions of the kidneys were pronounced, and normokalemic urine could mean.

Renal dysplaasia in human is often associated with a variety of organ malformations (Perez and Lewis 1982, Enderl and Geirig 1997). These malformations are presumed to be a heterogeneous collection of disorders, and their pathophysiology is intricate. Vascular disruption during early development may explain some of the cases associated with pathological anomalies, although these cases may also be associated with genetic defects (Severi and Fries 1995). In the experience of the current authors, renal dysplaasia in dogs may also be associated with multiple organ malformations, such as truncus arteriosus, renal aplasia, and renal hypoplasia.

Renal dysplaasia has been described together with congenital heart defects in two broiler strain (Darre-rin and others 1995). Reports of Fanconi syndrome in dogs commonly describe young adults as having no other recognized renal disease. In the present report, lesions characteristic of renal dysplaasia, with focal glomeruli and segmental necrotizing atrophy of the nephrons, were described. It was not determined in the cases described by Darre-rin and others (1995) whether the renal tubular lesions 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 such animals may be correlated with the regional distribution of the disease, and with the part of the tubules which is most severely affected.

Conclusions

It can be concluded from the case 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.