Use of proligestone in the management of three German shepherd dogs with pituitary dwarfism

Three German shepherd dogs were diagnosed with pituitary dwarfism and subsequently treated with proligestone. Treatment resulted in development of an adult hair coat, increased bodyweight and elevated insulin-like growth factor-1 concentration. Two dogs received thyroid supplementation during proligestone therapy. Adverse effects (cystic endometrial hyperplasia and acromegaly) were reported in two cases. No side effects were reported in the remaining case. This is the first report of the use of proligestone in the management of pituitary dwarfism.

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INTRODUCTION

Pituitary dwarfism is caused by a lack of growth hormone that results in proportionate dwarfism. In German shepherd dogs, the condition is thought to be inherited as an autosomal recessive gene (Andresen and Willeberg 1976, Nicholas 1978). Lesions in the pituitary gland are thought to be responsible for the deficiency of growth hormone (Rao and Baht 1971, Capen 1983). However, pituitary cyst formation may be a secondary feature to the defect in growth hormone production (Hamann and others 1999). Pituitary cyst formation can result in deficiencies of other anterior pituitary hormones (thyroid-stimulating hormone [TSH], adrenocorticotropic hormone [ACTH], follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) (Feldman and Nelson 1996) and neurohypophyseal dysfunction (antidiuretic hormone deficiency) (Ramsey and others 1999).

The use of progestins has recently been shown to induce the production of growth hormone from cell of hyperplastic ductular epithelium of the mammary gland (Mol and others 1984, 1996). These progestin-induced increases in growth hormone are also associated with elevated plasma concentrations of insulin-like growth factor 1 (IGF-1) (Mol and others 1996, 1997). Administration of medroxyprogesterone acetate to two German shepherd dog pituitary dwarfs has been shown to increase bodyweight and induce the development of adult hair coat (Kooistra and others 1998). This is the first report of the use of proligestone, a synthetic progestagen, for the management of pituitary dwarfism in dogs.

CASE HISTORIES

Two female and one male German shepherd dogs were referred to the University of Glasgow Veterinary School (case 1) and the Queen’s Veterinary School Hospital, University of Cambridge (cases 2 and 3) with suspected pituitary dwarfism. All three dogs were undersized for their age (Table 1) but there was no evidence of disproportionate limb growth. The dogs had retained puppy coat and alopecia over the caudal dorsum, elbows, stifles and tail (Fig 1). Both females had been in season more than one month prior to referral; case 1 had been in season at four months of age and again at two weeks prior to referral. Thirst, urination and defaecation were normal in all three dogs. Appetite was normal in case 1, but was considered reduced in cases 2 and 3. Marked brachygnathism was evident in cases 1 and 2. Case 2 was nervous but no other behavioral problems were noted in any of the dogs.

Table 1. Age, sex and weight of the dogs at presentation

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age (months)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Normal weight for age (kg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>F</td>
<td>11.0</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>F</td>
<td>9.4</td>
<td>27.3</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>M</td>
<td>76.0</td>
<td>76</td>
</tr>
</tbody>
</table>

*Normal weight of a female German shepherd dog (Randolph and others 1990)
* Female, M Male

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Congenital growth hormone deficiency was suspected on the basis of the proportionate dwarfism, brachygnathism and retained puppy hair coat. Serum concentrations of IGF-1 were subnormal (Table 2), confirming pituitary dwarfism in all three dogs (Eigenmann and others 1984). Serum cortisol concentrations were measured before and 30 minutes after intravenous injection of 0.25 mg of tetracosactrin (Synacthen; Alliance Pharmaceuticals). Serum thyroxine (T₄) concentrations were measured before and four hours after intravenous administration of 200 µg of thyrotrophin-releasing hormone (TRH).
hormone (TRH, Cambridge Laboratories). Canine thyroid-stimulating hormone (TSH) concentrations were measured before and 30 minutes after TRH administration (Scott-Moncrieff and Nelson 1988). The results of endocrine testing are shown in Table 2.

Treatment with progesterone (Delvotest; Intervet UK) by subcutaneous injection at 10 mg/kg every three weeks was instituted once the diagnosis of pituitary dwarfism was confirmed (cases 1 and 2) or after thyroid therapy failed to result in a significant improvement in coat quality (case 3). Case 1 was treated with progesterone alone. Case 3 was initially treated with thyroxine (Soluoxine; Arnold's Veterinary Products) alone at a dose of 0.02 mg/kg twice daily orally for 37 weeks prior to progesterone therapy. Case 2 received concurrent thyroxine treatment at a dose of 0.02 mg/kg once daily orally during progesterone therapy. Thyroid supplementation was continued after progesterone therapy was withdrawn in cases 2 and 3. At each visit any change in weight, hair coat, thry, appetite or urination was recorded. The mammary glands were palpated and the vulva was examined for discharge. Blood was collected for measurement of serum IGF-1 concentrations (Fig 2).

No mammary development or other adverse effects were recorded during therapy in case 1. Mammary development was noted in cases 2 and 3 after 12 and 9 weeks, respectively. Treatment with progesterone was withdrawn from week 48 in case 2 due to the development of heavy breathing at exercise. Treatment was re-instituted at week 68 but withdrawn again from week 81 due to development of the clinical features of acromegaly (increased soft tissue formation around the head and neck, inspiratory stridor, enlargement of the limbs, heavy muscle development and increased interdigital spaces).

Case 3 developed a recurrent bacterial pyoderma after 16 weeks which was treated with a variety of antibiotics including ampicillin (Amfipen; Intervet UK), cephalixin (Ceporex; Schering-Plough Animal Health) and enrofloxacin (Baytril; Bayer). Features of acromegaly were detected 28 weeks after the start of treatment in case 3 (Fig 3) and treatment was therefore withdrawn for 20 weeks. Treatment was re-instituted at 46 weeks due to a rise in IGF-1 concentration (Fig 2C). However, treatment was withdrawn again from week 60 due to a recurrence of the signs of acromegaly. Case 2 developed a recurrent vulval discharge 87 weeks after starting therapy. Ovariohysterectomy was performed at week 96 and the presence of cystic endometrial hyperplasia was confirmed on histopathology. Case 3 was castrated at 117 weeks due to recurrence of hair loss (oestrogen and androgens have been shown to suppress initiation of the anagen phase of the hair cycle in rats; Scott and others 1995).

During the treatment of case 1, the dose of progesterone was gradually increased from week 14 as no adverse effects had been reported and treatment had failed to increase IGF-1 concentrations to any marked degree. The dose was maintained at 15 mg/kg from week 20 of treatment. A voided urine sample was collected at 35 weeks to determine if glucocorticoids were present. Dipstick analysis showed no abnormalities; specific gravity was 1.024. No adverse side effects were reported during treatment. Total 14 concentrations were measured intermittently in all dogs and basal TSH in cases 2 and 3 (Table 3).

Improvement in the coat quality was noted within 10 weeks of starting treatment in all three cases (Fig 4). Primary hairs initially developed over the tail and subsequently appeared over the dorsum and flanks. Hair regrowth at sites of clipping was noted by week 14 in case 1. A recurrence of hair loss was noted in case 2 after progesterone therapy had been withdrawn for 10 weeks and in case 3 after therapy had been withheld for 14 weeks. All dogs showed a steady increase in bodyweight during treatment and even after treatment had been withdrawn in cases 2 and 3 (Fig 5). An increase in pwe size was noted in case 1 at 10 weeks.

![FIG 2. Appearance of case 2 at 26 weeks. The increased soft tissue around the head and neck and forelimb thickening are consistent with the development of acromegaly](image-url)
FIG 4. Appearance of the dogs during and after treatment:
(A) Case 1 at four weeks. The puppy hair coat still predominates but primary hairs are evident over the hind quarters. Alopecia is evident over the stifle. Hair clipped from the jugular area has failed to regrow.
(B) Tail and hindquarters of case 1 at four weeks. Primary hairs are growing down the length of the tail and over the hindquarters. The area of alopecia on the tail has reduced in size compared to the pre-treatment appearance.
(C) Case 1 at nine weeks. The tail has an adult appearance and is completely covered with primary hairs. The growth of primary hairs over the dog’s body has increased dramatically. Primary hairs now predominate over the dorsum and flanks.
(D) Case 2 at 13 weeks. Primary hair growth is evident on the face, forelimbs and tail. Some increase in primary hair growth is evident on the trunk.
(E) Case 2 at 64 weeks. The dog has developed a full adult hair coat. A dramatic improvement in hair growth was noted three weeks after autotransplantation.
(F) Case 3 at 113 weeks. The dog has developed a full adult hair coat.

DISCUSSION

Pituitary dwarfism is caused by a failure of production of growth hormone by the anterior pituitary lobe. The condition is often associated with other endocrine abnormalities including failure of ACTH and TSH production (Feldman and Nelson 1996, Kooistra and others 2000). Canine growth hormone treatment is not available for therapeutic use. Studies using heterologous non-canine growth hormone have shown an increase in secondary hair growth with little effect on primary hair growth (Kooistra and others 1999); there is the additional disadvantage that biosynthetic human growth hormone administration in the dog results
in the production of antibodies against growth hormone (van Herpen and others 1994). The majority of pituitary dwarfs therefore, receive only thyroid supplementation and/or glucocorticoids as indicated by the results of endocrine testing.

The use of progestins has recently been shown to induce the production of growth hormone from foci of hyperplastic ductular epithelium of the mammary gland (Mol and others 1994, 1996). These progestin-induced increases in growth hormone are also associated with elevated plasma concentrations of IGF-1 (Mol and others 1996, 1997). Treatment of canine pituitary dwarfs with medroxyprogesterone acetate at doses of 2.5 to 5.0 mg/kg bodyweight has been reported to improve hair coat and increase body size, but is associated with the development of intermittent pyoderma and cystic endometrial hyperplasia (Kooistra and others 1998). The increase in bodyweight and the development of an adult hair coat, seen in the present three cases, is similar to that reported previously (Kooistra and others 1998). The dramatic improvement reported after ovariohysterectomy and castration in cases 2 and 3, respectively, was attributed to removal of estradiol and progesterone which have been shown to suppress the initiation of the anagen phase of the hair cycle in rats (Scott and others 1995).

Cases 2 and 3 received oral thyroxine supplementation during administration of progestogen and case 3 had also received thyroxine for 21 weeks prior to progestogen therapy. Thyroid administration can cause an increased rate of hair growth in dogs without hypothyroidism (Gunaratnam 1986, Muller and others 1989). The coat changes seen in these patients may have been related to thyroid supplementation, although this explanation does not seem likely based on the time scale. The dramatic response seen in case 1 and the further improvement in coat quality noted in case 3 would suggest that the improvement in hair coat was due to administration of progestogen and not solely to thyroid supplementation.

Pituitary cyst formation can result in deficiencies of other anterior pituitary hormones (Feldman and Nelson 1996) and neurohypophyseal dysfunction (Ramsey and others 1999). Magnetic resonance imaging and computed tomography studies can be used to confirm the presence of a pituitary cyst. These investigations were not performed as they require general anaesthesia and the results would not have altered the treatment options. The results of the ACTH stimulation test in all three cases revealed no evidence of glucocorticoid deficiency. Thyroid axis function was assessed using the T4 and TSH responses to intravenous TRH. Basal TSH concentrations were undetectable in cases 2 and 3. In both these cases, TSH concentrations failed to increase after administration of 100 μg TSH, suggesting a possible diagnosis of secondary hypothyroidism (pituitary failure of TSH release). Thyroid supplementation was therefore administered prior to (case 3) and/or concurrently with progestogen therapy (cases 2 and 3). Basal TSH was elevated in case 1 and increased by only 6.5 μU/ml following TRH administration, while T4 failed to increase following TRH, suggesting that this dog was suffering from primary hypothyroidism (thyroid gland failure of thyroid hormone release) (Scott-Moncrieff and Nelson 1998). Thyroid supplementation was withheld as TSH concentrations were normal and further assessment of basal T4 was performed at weeks 7 and 27.

After treatment with progestogen, serum total T4 concentrations increased in case 1. This may have been associated with the dog's reproductive status as it was reported to have been in oestrus two weeks prior to endocrine testing. Females in oestrus have elevated concentrations of total T4 compared to females at other stages of the reproductive cycle (Riemers and others 1984, 1990). This may have resulted in a false elevation of total T4 concentration at week 7. Alternatively, administration of progestogen may have resulted in an increase in T4 at weeks 1 and 27, since endogenous progestrone is known to increase T4 and T3 concentrations (Riemers and others 1984, 1990). Although post-treatment thyroxine was also assessed in cases 2 and 3, both were receiving thyroid supplementation at the time of sampling, which makes interpretation of these results difficult.

The response of serum TSH to TRH administration in pituitary dwarfs appears to be highly variable. Ramsey and others (1997) diagnosed secondary hypothyroidism in one pituitary dwarf with a TSH concentration of <0.1 ng/ml, which increased to 0.2 ng/ml after TRH. Scott Moncrieff and Nelson (1998) reported a pituitary dwarf with an increase in TSH concentration from 0.03 ng/ml to 0.57 ng/ml following TRH, a result consistent with euthyroidism. This post-TRH TSH concentration is similar to that of case 1 in this study. With the advent of new methods of assessing the thyroid axis, such as cTSH assays, further studies are required to determine which cases of pituitary dwarfism are associated with thyroid dysfunction and whether administration of progestogen results in a change in thyroid axis function.

Progestogen was selected as the progestin of choice due to the absence of mammary or uterine disease associated with its use (Evans and Sutton 1989). Medroxyprogesterone acetate administration has been associated with a high incidence of cystic endometrial hyperplasia and pyometra and is therefore not recommended for use in an intact bitch (von Berky and Townsend 1993). Despite the reported apparent safety of progestogen, its use was associated with cystic endometrial hyperplasia in one of the bitches treated in this study.

The initial dose of progestogen used in these cases (11 μg/kg) was based on the dose recommended in the manufacturer's (Intervet UK) data sheet for postponement of oestrus. The dosing interval (three weeks) was based on previous recommendations (Kooistra and others 1998). In humans with growth hormone deficiency, the dose of growth hormone required is based on serum IGF-1 concentration prior
to treatment (Murray and others 2003). Further studies are required to determine if pre-treatment IGF-I concentrations can be used to determine the dose of progestogen required in canine pituitary dwarfs. IGF-I is produced and released by the liver. Its secretion is under direct control of growth hormone. IGF-I has been reported to be a more sensitive indicator of the effect of treatment than growth hormone concentrations as the latter is released in a pulsatile manner (Kooistra and others 1998). Serum IGF-I concentrations were therefore used to monitor the response to treatment. Since stimulation of growth hormone secretion by progestins appears to be dose related (Scott and Concannon 1983), the dose of progestogen was increased in case 1 when the IGF-I concentration failed to increase above 100 ng/ml. This dose was associated with an increase in IGF-I concentration to over 100 ng/ml. Further studies are required to determine if IGF-I concentration during treatment should be used to determine the dose of progestogen. In this study, the results of the IGF-I assay were available only two to three weeks after collection. Treatment was therefore altered on the basis of the serum IGF-I concentration from the previous visit. The dose of progestogen was increased in an attempt to bring the IGF-I concentration into the normal range for an adult German Shepherd dog (>200 ng/ml). The IGF-I results, however, never exceeded 200 ng/ml.

Adverse effects were noted in cases 2 and 3 and were thought to be related to increases in growth hormone (acromegaly) and direct progestogen effects (vulval discharge and cystic subcutaneous hypoplasia). Papules and secondary bacterial pyoderma frequently develop in the adult pituitary dwarf and are probably a result of altered skin immunity (Feldman and Nelson 1995) rather than the use of a progestin. Clinical signs consistent with acromegaly were noted after the IGF-I concentration exceeded 200 ng/ml on two consecutive samples. These side effects have previously been attributed to the continuous production of growth hormone by the mammary gland following progestogen therapy (Kooistra and others 1998). Growth hormone secretion from the normal pituitary gland is pulsatile (Vanwam and others 1987), whereas its secretion from the mammary gland is continuous which may more easily result in an increased total daily secretion (Yoshihara and others 1995) with an increased risk of side effects. Withholding progestogen therapy appeared to be associated with a reduction in IGF-I concentration. The absence of adverse effects in case 1 could reflect the relatively low levels of growth hormone and IGF-I achieved during treatment or the difficulty in diagnosing subclinical side effects. Further studies are required to determine the dose rate and frequency that will optimise development of an arthritic coat and increased body weight while minimising the risk of adverse effects.

Conclusions
This is the first report of the use of progestogens in dogs diagnosed with pituitary dwarfism. Prolactinosten may provide an alternative, relatively cheap treatment, which, if monitored carefully, could induce fewer adverse effects than other progestins. Based on the results presented here, treatment should be tailored to ensure that IGF-I concentration does not exceed 200 ng/ml. Further studies are required to determine the optimum dose, the optimum age at which treatment should be instigated, how long therapy should be maintained and whether progestogens have an effect on thyroid axis function in pituitary dwarfs.

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References
