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Spontaneous acromegaly: A retrospective case control study in German shepherd dogs

F. Fracassi [a,*], L. Zagnoli [a], D. Rosenberg [b,c], T. Furlanello [d], M. Caldin [e]

[a] Department of Veterinary Medical Sciences, Bologna University, Via Tolara di Sopra 50, 40064 Ozzano dell'Emilia, Bologna, Italy
[b] Internal Medicine Unit, Université Paris-Est, Ecole Nationale Vétérinaire d'Alfort, Maisons-Alfort, France
[c] Micen Vet Centre, Créteil, France
[d] Laboratorio Veterinario San Marco, Padova, Italy
[e] Clinica Veterinaria San Marco, Padova, Italy

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ABSTRACT

Acromegaly results from the overproduction of growth hormone in adulthood and is characterised by overgrowth of soft tissue and/or bone as well as insulin resistance. There are few data indicating the risk factors associated with this disease in dogs or its clinicopathological features and sequelae. The objective of this retrospective study was to catalogue and assess these aspects of the disease in German shepherd dogs (GSDs) which were found to be over-represented among acromegalic dogs attending two veterinary referral clinics over a period of 7 years. Each acromegalic dog (AD) was compared with two breed/age/sex matched controls.

Clinical signs of acromegaly included panting, polyuria/polydipsia, widened interdental spaces, weakness, inspiratory stridor, macroglossia, weight gain, redundant skin folds, thick coat, exophthalmos and mammary masses. Serum alkaline phosphatase, creatine-kinase, glucose, triglyceride, phosphate ion, and 'calcium per phosphate product' concentrations were significantly higher in acromegalic animals while haemoglobin concentration, blood urea nitrogen, sodium and chloride ion concentrations, and urinary specific gravity, osmolality and fractional excretion of phosphate were significantly lower. Although, in the majority of cases clinicopathological abnormalities resolved following ovariohysterectomy, in one dog, acromegalic signs abated and insulin-like growth factor-1 concentrations normalised only following the surgical excision of mammary tumours carried out 2 months after ovariohysterectomy. The findings of this study indicate that GSDs are predisposed to the development of acromegaly with a suspected inherited susceptibility.

Introduction

Acromegaly is a chronic endocrine disorder characterised by overgrowth of soft tissue and/or bony structures and insulin resistance due to growth hormone (GH) overproduction in adulthood. The pathogenesis of acromegaly differs between dogs and cats. In cats, as in humans, the disease results from excessive GH secretion from a pituitary adenoma (Rijnberk et al., 2003) whereas in dogs it is most commonly progesterone-induced: in middle-aged/elderly bitches, either endogenous progesterone (during the luteal phase of oestrous cycle) or exogenous progestins (as used in oestrus prevention) may give rise to GH hypersecretion of mammary origin (Kooistra, 2010). In rare cases, a pituitary somatotroph adenoma may cause acromegaly in dogs (Fracassi et al., 2007). Canine hypothyroidism is associated with elevated serum GH concentrations and physical changes akin to those occurring in acromegaly (Lee et al., 2001).

Spontaneous progesterone-induced acromegaly in dogs has been reported only rarely (Eigenmann and Venker-van Haagen, 1981; Eigenmann et al., 1983, 1984; Selman et al., 1991; Jensen et al., 1993; Villforth, 1998; Norman et al., 2006) and there is little information regarding breed predisposition or clinicopathological features, although there is some anecdotal evidence that German shepherd dogs (GSDs) are overrepresented. The objective of the present study was to describe the breed predisposition, clinical features and laboratory findings of acromegaly at the time of diagnosis and following ovariohysterectomy.

Materials and methods

Study population

The clinical records of GSDs diagnosed with acromegaly between August 2004 and August 2011 at the San Marco Veterinary Clinic in Padua (Italy) and the Department of Veterinary Medical Sciences at the University of Bologna (Italy)

* Corresponding author. Tel.: +39 0512097590.
E-mail address: federico.fracassi@unibo.it (F. Fracassi).

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were assessed retrospectively. In addition to full clinical examinations, routine haematological and biochemical assessments were performed including the measurement of serum progesterone, insulin-like growth factor (IGF)-1, free thyroxine (T4), thyrotropin concentrations (cTSH), and urinalysis (including measurement of calcium and phosphate excretion). All analyses were performed at the San Marco Veterinary Laboratory within 24 h of sample collection.

One clinically normal control dog (HCD) and one clinically affected animal (SCD) (see details below) were included for each acromegalic dog (AD). These dogs were matched for age (±6 months) and were all intact female GSDs. Clinically affected controls were GSDs with conditions other than acromegaly: four with mammary tumours, two with chronic enteropathy, two with chronic dermatopathy, and individual animals with pyometra, chronic renal disease, gastric foreign body, cystic endometrial hyperplasia, megaoesophagus, chronic bronchitis, Cushing's disease and intervertebral disk extrusion.

Diagnostic criteria

The clinical records of all dogs presented at the San Marco Veterinary Clinic and at the University of Bologna between August 2004 and August 2011 were reviewed. Included dogs exhibited widened interdental spaces and at least two other characteristic clinical signs of inspiratory stridor, panting, excessive skin folds, thick hair coat, polyuria/polydipsia (PU/PD), generalised weakness, increased bodyweight and macroglossia. Where animals showed no evidence of increased inter-dental spaces they had to demonstrate at least four of these characteristic signs. Inclusion criteria also required that dogs had serum IGF-1 concentrations greater than the upper limit of the reference range (137–425 ng/mL). Dogs that had been given progestins within the previous 12 months were excluded from the study.

Laboratory examinations

Complete blood counts and clinical biochemistry profiles were carried out on each selected dog using an ADVIA 2120 automatic cell counter (Bayer) and an automated analyser (Olympus AU2700), respectively. The biochemistry panel included the following parameters: creatine-kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (Tot Bil), total serum protein (Tot Prot), albumin (Alb), cholesterol, triglyceride, amylase, lipase, urea, creatinine, glucose, calcium, inorganic phosphate, sodium, potassium, chloride, total iron (Fe), unsaturated iron binding capacity (UIBC) and C reactive protein (CRP).

Some analytes were calculated, namely, globulin (Glob) (Tot Prot minus Alb), phosphate × calcium, total iron binding capacity (TIBC) (Fe added to UIBC), saturation percentage of iron (Sat %) (Fe × 100/TIBC) and urinary fractional excretion of phosphate and calcium. Serum IGF-1 and progesterone were measured using an automated solid-phase, enzyme-labelled chemiluminescent immunometric assay (Immulite 2000 IGF-1 assay, Diagnostic Products) (Chapwanya et al., 2008; Tvarijonaviciute et al., 2011).

The intra- and inter-assay coefficients of variation (CVs) and sensitivity were, respectively, 3.7%, 6.3% and 20 ng/mL for the IGF-1 assay, and 7.1%, 9.9%, and 0.2 ng/mL for the progesterone assay. Serum free T4 and thyrotropin (cTSH) concentrations were measured using the same equipment (Iversen et al., 1999; Scott-Moncrieff et al., 2011). Intra- and inter-assay CVs and assay sensitivities were 5.7%, 6.3%, and 4 pmol/L, and 7.6%, 7.2%, and 0.01 ng/mL, respectively.

The reference ranges reported in the present study were obtained from data from 40 healthy GSDs using the 'robust method' described in *Clinical and Laboratory Standards Institute Guidelines* (Horowitz, 2010). Reproductive tract ultrasonography, ovariohysterectomy, mastectomy and histopathological examinations were carried out following standard procedures.

Statistical analysis

The prevalence of acromegaly with 95% confidence intervals (CI) was calculated for the overall population and for intact females. To determine if a breed predisposition existed, the incidence in GSDs in both clinics (number of dogs diagnosed between 2004 and 2011/total number of intact female GSDs admitted over this period) was compared with the overall incidence of acromegaly in intact females of all breeds (number of cases in females between 2004 and 2011/number of total intact females admitted over this period). This comparison was performed using the χ^2-test.

The D'Agostino test was used to assess the normality of the data, and where not normally distributed, differences between groups were assessed using the Kruskal–Wallis test: post-test analysis was performed using a Bonferroni test. The Mann–Whitney *U*-test determined if ADs or HCDs differed significantly in terms of IGF-1. Data were given as medians and ranges and $P < 0.05$ was considered significant.

Fig. 1. Photographs of a 10 year old intact female German shepherd dog with acromegaly. (A) Excessive skin folds, thick hair coat, and macroglossia; and (B) enlarged interdental spaces.

Results

Incidence, breed predisposition and clinical findings

A dataset of 34,380 dogs of various breeds and sex was identified containing 14 intact females with, and 9204 without, acromegaly: 11 and 656 intact female GSDs with and without acromegaly, respectively, were included. Of the 205 different breeds (including mixed breed dogs), four were represented by at least one intact female with acromegaly. The incidence within the overall population was 0.04% (95% CI; 0.02–0.07%). The incidence within the overall intact female population was 0.15% (95% CI; 0.08–0.25%). The incidence within the intact female GSD population (1.65%, 95% CI; 0.81–2.92%) was significantly higher ($P < 0.0001$) than that in the overall female population. Of the GSDs with acromegaly, there were two different pairs of littermates.

At initial presentation, the median age of ADs was 10 years (range, 4–14 years). The median bodyweight was 46 kg (35–58 kg) and was significantly higher than that of HCDs (32 kg, 26–36 kg) and SCDs (33 kg, 24–40 kg). The median body condition score of ADs was 6/9 (5/9–7/9). Ten of 11 dogs presented with excessive panting, PU/PD was reported in 8/11 cases, generalised weakness in 5/11, stridor in 6/11, and weight gain in 5/11. Excessive skin folding (Fig. 1) was evident in 4/11 animals and 5/11 dogs were reported to have thickened coats. Widened inter-dental spaces were reported in 6/11 (Fig. 2), macroglossia in 4/11, and exophthalmos in 3/11 (Fig. 3).