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Cushing's syndrome—an epidemiological study based on a canine population of 21,281 dogs

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Abstract
The epidemiological characteristics of spontaneous hypercortisolism (HC) were derived from 21,281 client-owned dogs selected from four private veterinary clinics and one university reference center for endocrinology. The odds ratio (OR) method was employed to investigate the risk of developing HC related to breed, gender, and sexual status. The estimated prevalence of HC in the four private clinics was 0.20% [95% confidence interval (CI), 0.13–0.27] and was significantly different compared to the university reference center (1.46%; 95% CI, 1.12–1.80). Sex, breed, and age resulted in risk factors for HC. Mean (± SD) age for dogs with HC was 9.8 (± 2.5) yr. Females had higher risk for HC compared to males (OR 1.85; 95% CI, 1.24–2.75); all neutered dogs (both males and females) had higher risk than intact dogs (OR 2.54; 95% CI, 1.72–3.73); and neutered females had higher risk compared to intact females (OR 2.61; 95% CI, 1.54–4.42). Using the mixed breed dogs as a control population (OR = 1), the risk of developing HC was significantly higher in the Standard Schnauzer (OR 58.1; $p < 0.0001$) and Fox Terrier (OR 20.33; $p < 0.0001$). With regard to HC, this study identified an overall prevalence of 0.20%. The data support the existence of sex predisposition, with the highest risk for neutered females.
Keywords: Cortisol, Hyperadrenocorticism, Hypercortisolism, PDH.

Introduction

Spontaneous hypercortisolism (HC), also known as Cushing's syndrome, is caused by a chronic and pathologic overproduction of cortisol and generally occurs in middle-aged to older dogs (Ling *et al*., 1979; Ortega *et al*., 1996; Gallelli *et al*., 2010). The excess of glucocorticoids causes a combination of physical and biochemical changes that have a considerable impact on the animal's quality of life. HC is either the result of pathological oversecretion of adrenocorticotropic hormone (ACTH) by a functional pituitary tumor (PDH, pituitary-dependent hyperadrenocorticism) or is the consequence of a primary adrenal disorder (ADH, adrenal-dependent HC) (Behrend, 2010). Recently, HC resulting from other causes (e.g., ectopic secretion of ACTH or food-dependent hypercortisolemia) has also been described in dogs but these seem to be rare conditions (Galac *et al*., 2005; 2008; Castillo *et al*., 2014). In humans, HC is considered a rare disease with an incidence ranging from 0.7 to 2.4 individuals per million population per year (Ambrosi *et al*., 1990; Lindholm *et al*., 2001). Clinical experience shows that HC is a fairly common endocrinopathy in dogs even if, to our knowledge, there are only a few epidemiological studies published in the literature. In the United States, the incidence of new cases of hyperadrenocorticism is 1 to 2 cases per 1,000 dogs per year, and the prevalence of PDH is estimated around 0.2% (Willeberg and Priester, 1982; Lourenço *et al*., 2015). A recent study performed in the United Kingdom reported an estimated prevalence of 0.28% for HC (O'Neill *et al*., 2016). A significant predisposition to HC in older dogs and in some breeds, such as miniature Poodle, Boxer, and Dachshund has been observed (Ling *et al*., 1979; Jensen *et al*., 1997; Burkhardt *et al*., 2013; Fracassi *et al*., 2015a; Van Rijn *et al*., 2016). A potential predisposition for female dogs has been reported in some studies (Ortega *et al*., 1996; Wood *et al*., 2007; Gallelli *et al*., 2010) but such studies suffer from the lack of a control population. Because of potential environmental and genetic differences across geography and time, these data may not be translatable to the current worldwide canine population. The aim of this study is to fill in the gaps in our epidemiological knowledge of HC through the analysis of a canine Italian population.

Materials and Methods

Data were extracted from client-owned dogs selected from electronic databases of five veterinary clinics for cases matching the search terms "hyperadrenocorticism," "Cushing's syndrome," "PDH/ADH," or "HC" between

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September 2012 and September 2014. The teaching hospital of the Department of Veterinary Medical Science, University of Bologna is a reference center for HC, while the other four 24-h clinics, scattered throughout the Italian territory (four in northern Italy and one in southern Italy) in order to avoid regional and local effects, were selected for the presence of an adequate electronic patient records system. The veterinarians of the different centers participating in the study had to fill in a questionnaire with signalment (breed, age, sex, and neuter status), anamnesis, physical examination, clinicopathological data, diagnostic imaging, and specific endocrine evaluations of dogs at the time of the diagnosis of HC.

Inclusion criteria for dogs with HC

To be enrolled in the study, a dog had to present with clinical signs compatible with HC (e.g., polyuria, polydipsia, polyphagia, enlarged abdomen, and symmetrical alopecia), laboratory findings consistent with HC (increased serum alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase, hypertriglyceridemia, hypercholesterolemia, hyperphosphatemia, thrombocytosis, lymphopenia, diluted urine, and proteinuria), and a positive result to at least one endocrine test between ACTH stimulation test (cortisol concentration 1 h after administration of 5 μg/kg of tetracosactide acetate IV >22 μg/dl was considered positive), low-dose dexamethasone suppression test (LDDST) or high-dose dexamethasone suppression test (HDDST). In some patients, these tests were combined with urine cortisol-to-creatinine ratio or with endogenous ACTH concentration. The medical records of the different clinics had been re-evaluated by a board-certified internist (F.F.) in order to confirm the conformance with inclusion criteria. The dogs were divided according to the list of dog breeds approved by the Italian Kennel Club (ENCI).

Control group

A control group was used to identify risk factors for HC by comparing the characteristics of dogs with HC with a population of dogs without HC. The control group included all dogs examined in the different centers of this study in the same time period mentioned above for any reason but without a diagnosis of HC. The subjects were divided according to the list of dog breeds approved by the ENCI.

Epidemiological investigation criteria

Both pre-existing cases (diagnosed with HC before data collection began) and incident cases (newly diagnosed with HC during the data collection period) were included in the prevalence estimate. This was calculated by dividing the number of HC cases by the total number of dogs attending participating clinics during the study period. The prevalence in the reference center was calculated separately. Standard methods were used to calculate the 95% confidence intervals (CIs) to indicate the precision of the estimate. To investigate the presence of a breed predisposition for HC, the prevalence was evaluated and compared with the control group only for those breeds that had at last two individuals with HC. The reported age was the one reported at the time of HC diagnosis. Similarly, to assess the gender predisposition, both dog populations (HC and control) have been divided according to their gender, with subgroups of neutered and intact.

Data analysis

Data were checked and cleaned in a spreadsheet (Microsoft Office Excel 2007, Microsoft Corp.) and exported to Prism® (GraphPad software) for further analysis. The prevalence of HC was calculated either on the overall population, on the University reference center, and on the private clinics population. To evaluate the breed-related risk of developing HC, the odds ratio (OR) was calculated for each breed by choosing mixed breed dogs as the reference breed (OR = 1). ORs were also calculated to estimate the effect of gender (males versus females, with male sex as reference) and sexual status (neutered versus intact, with neutered as a reference). The statistical significance of the computed risk was evaluated through Fisher's exact test with a 95% significance level ($p < 0.05$), and CIs were also reported.

Results

Demographics and prevalence

The overall dataset comprised of 21,281 dogs attending five clinics in Italy between September 2012 and September 2014. From the whole population, 104 dogs were identified with HC on the basis of history, clinical and laboratory findings, and positivity to at least one endocrine test. Table 1 reports the partition of the dataset between the various clinics. The estimated prevalence for HC in the four private clinics was 0.20% (95% CI, 0.13–0.27) and was significantly different compared to the University reference center (1.46%; 95% CI, 1.12–1.80).

Signalment

Age data were available for only 91 of 104 dogs with HC. Mean (± SD) age for dogs with HC was 9.8 (± 2.5) yr, and only 5 of 91 dogs (5.5%) were ≤ 5 yr old. Gender data (Table 2) were available for all 104 dogs with HC and only for 19,059 of 21,177 dogs in the control group. Of 104 dogs with HC, 19.2% were intact females, 43.3% were neutered females, 29.8% were intact males, and 7.7% were neutered males. In the control group, 10,015 were male (52.5%) and 9,044 were females (47.5%). More specifically, 8,663 were intact males (45.4%), while 4,857 were intact females (25.5%), 4,187 were neutered females (22%), and 1,352 were neutered males (7.1%). Overall, considering sex regardless of neutered status, 62.5% were females and 37.5% were males. Females had higher risk for HC compared to males (OR 1.84; 95% CI, 1.24–2.75); neutered dogs had higher risk than intact dogs (OR 2.54; 95% CI, 1.72–3.73); and neutered females had a higher risk compared to intact females (OR 2.61; 95% CI, 1.54–4.42) (Table 2). No difference was noted between neutered and intact males.

Of the 32 different breeds (including the mixed breed category) of dogs with HC admitted to the five clinics over the period of the study, 16 (including the mixed breed category) had at least two dogs with HC and were, therefore, included in the analysis. Using the mixed breed dogs as a control population (OR = 1), the risk of developing HC was significantly higher in the Standard Schnauzer (OR 58.1; $p < 0.0001$), Fox Terrier (OR 20.33; $p < 0.0001$), Cavalier King Charles Spaniel (OR 8.03; $p < 0.0001$), Boxer (OR 7.67; $p < 0.0001$), ShihTzu (OR 6.56; $p = 0.0033$), Bolognese (OR 6.30; $p < 0.0001$), pit bull (OR 5.98; $p = 0.0009$), Jack Russell Terrier (OR 5.65; $p = 0.0081$), Maltese (OR 4.90; $p = 0.001$), Miniature Dachshund (OR 3.52; $p = 0.0027$), Miniature Poodle (OR 3.44; $p = 0.0033$), and Yorkshire Terrier (OR 3.43; $p = 0.0018$) (Table 3).

Discussion

The current study identified an estimated prevalence of HC in the four private clinics of 0.20% (95% CI, 0.13–0.27) that was different compared to the 1.46% (95% CI, 1.12–1.80) reported for the University referral center. The reasons for this discrepancy are quite obvious because the reference center receives more cases of suspected HC. The estimated prevalence of 0.20% is similar to the 0.28% observed in a study comprising 119 primary-care veterinary practices in the United Kingdom (O'Neill *et al*., 2016).

The median age at diagnosis of HC of 9.8 (± 2.5) yr was in agreement with the literature information that reported HC as a disease of middle-age and older dogs with a median value of approximately 9–11 yr (Jensen *et al*., 1997; Barker *et al*., 2005; Gallelli *et al*., 2010; Burkhardt *et al*., 2013; Fracassi *et al*., 2015a; Van Rijn *et al*., 2015; 2016; O'Neill *et al*., 2016).

In previous studies, the female population was either overrepresented (percentages between 55% and 75%) (Reusch and Feldman, 1991; Hanson *et al*., 2007; Gallelli *et al*., 2010; Helm *et al*., 2011; Burkhardt *et al*., 2013; Arenas *et al*., 2014; Fracassi *et al*., 2015a; 2015b; Macfarlane *et al*., 2016) or underrepresented (percentages between 27% and 50%) (Jensen *et al*., 1997; Hess *et al*., 1998; Barker *et al*., 2005; Bell *et al*., 2006; Van Rijn *et al*., 2016). Nevertheless, the lack of a control group in all of these studies, with the exception of O'Neill *et al*. (2016), makes it hard to establish a conclusive relationship between gender and HC. In the current study, which included a control group, the results show that sex seems to be a risk factor for HC with female-to-male OR of 1.85 (95% CI, 1.24–2.75). Furthermore, neutered dogs had a higher risk than intact dogs (OR 2.54; 95% CI, 1.72–3.73); and neutered females had a higher risk compared to intact females (OR 2.61; 95% CI, 1.54–4.42). The only other study with a control group failed to identify both sex and neutered status as risk factors (O'Neill *et al*., 2016).

Table 1. Overall dataset of dogs with HC and control group.

	University referral centre	Clinic 1	Clinic 2	Clinic 3	Clinic 4	Total
Dogs with HC	71	10	13	3	7	104
Control group	4,787	3,849	8,265	2,789	1,487	21,177
Total	4,858	3,859	8,278	2,792	1,494	21,281
Prevalence % (± CI)	1.46 (± 0.34)	0.26 (± 0.16)	0.16 (± 0.27)	0.11 (± 0.12)	0.46 (± 0.35)	

CI: confidence interval.

Table 2. Sex status of dogs with HC compared with dogs in the control group and relative OR.

Sex status	Dogs with HC	Control group	OR (CI)	*p* value
Male	39	10,015	1	NA
Females	65	9,044	1.85 (1.24–2.75)	0.0025
Intact	51	13,520	1	NA
Neutered	53	5,539	2.54 (1.72–3.73)	<0.0001
Intact females	20	4,857	1	NA
Neutered females	45	4,187	2.61 (1.54–4.42)	0.0004
Intact males	31	8,663	1	NA
Neutered males	8	1,352	1.65 (0.76–3.6)	0.2

NA: not applicable; CI: confidence interval.

Table 3. Breed distribution of dogs with HC compared with dogs in the control group and relative OR.

Breed	Dogs with HC	Control group	OR (CI)	*p*-value
Crossbred	33	6,709	1	NA
Standard Schnauzer	2	7	58.1 (11.63–290.10)	<0.0001
Fox Terrier	2	20	20.33 (5.57–90.50)	<0.0001
Cavalier King Charles Spaniel	3	76	8.03 (2.41–26.73)	<0.0001
Boxer	4	106	7.67 (2.67–22.04)	<0.0001
Shih Tzu	2	62	6.56 (1.54–27.93)	0.0033
Bolognese	4	129	6.30 (2.20–18.05)	<0.0001
Pitbull	3	102	5.98 (1.80–19.81)	0.0009
Jack Russell Terrier	2	72	5.65 (1.33–23.98)	0.0081
Maltese	4	166	4.90 (1.72–13.99)	0.001
Miniature Dachshund	6	347	3.52 (1.46–8.45)	0.0027
Miniature Poodle	6	355	3.44 (1.43–8.25)	0.0033
Yorkshire Terrier	7	415	3.43 (1.51–7.80)	0.0018
Labrador	5	408	2.49 (0.97–6.42)	0.05
German Shepherd	2	284	1.43 (0.34–6.00)	0.62
Beagle	2	623	0.65 (0.16–2.73)	0.5

NA: not applicable; CI: confidence interval.

In human medicine, HC has a substantial female over-represented but the cause for this predisposition remains unclear (Boscaro *et al*., 2001; Huan *et al*., 2014). In humans (Lacroix *et al*., 2001; Christopoulos *et al*., 2005), in mice (Bernichtein *et al*., 2009), and in ferrets (Schoemaker *et al*., 2008), there are different reports of luteinizing hormone receptor (LHR)-mediated HC. In ferrets, it is known that gonadectomy induces LHR-dependent adrenal hyperplasia and tumorigenesis, probably triggered by the elevated luteinizing hormone (LH) levels post-gonadectomy. The results of a study in dogs seem to indicate that overexpression of LHR was not responsible for HC and adrenocortical tumorigenesis but the potential functional role of LH remains to be elucidated (Galac *et al*., 2010).

Dachshunds, Terriers, and Boxers have been identified to have a significantly higher risk of developing HC, and similar conclusions were reached by many other studies (Ling *et al*., 1979; Jensen *et al*., 1997; Bell *et al*., 2006; Hanson *et al*., 2007; Helm *et al*., 2011; Rodriguez Piñeiro *et al*., 2011; Burkhardt *et al*., 2013; Fracassi *et al*., 2015a; 2015b; Van Rijn *et al*., 2015; 2016; O'Neill *et al*., 2016). In the present study, this finding has been confirmed and reinforced. In the present study, the Standard Schnauzer was identified as the breed with the highest OR (58.1), while the risk associated with this breed in other studies was much lower (Ling *et al*., 1979; Hanson *et al*., 2007; Helm *et al*., 2011; Fracassi *et al*., 2015a; 2015b; O'Neill *et al*., 2016; Van Rijn *et al*., 2016). Conversely, there are breeds which were not represented in this study but have been found to have a significant OR; for example, O'Neill *et al*. (2016) reported an elevated OR for Bichon Frisé (OR 6.5), which was not part of the examined population of this study. The reason for the differences between the results of our study and those of other previously published reports could be due to either the different distribution/representation of canine breeds in different geographic areas or to the descriptive features of other studies that did not take into account the prevalence of the different breeds. While there are overlaps, none of the studies investigate the same set of breeds. For example, our study found a high OR in the Bolognese (6.30) and pit bull (5.98), which were not described as predisposed breeds in the literature.

The main limitation of the present study is its limited spatial and temporal coverage. With only five clinics, it was not possible to cover extensively the Italian territory; and, with only two yr of temporal coverage, it was not possible to estimate the incidence of HC over time. Finally, another issue faced during this study regarded the missing data in the clinical records. In fact, there were some cases where the four private clinics did not record the age of some dogs.

Nevertheless, this is one of the first epidemiological studies on canine HC, along with O'Neill *et al*. (2016), taking into account a control population in order to generate meaningful statistics of predisposition. The results from this study are in agreement with the existing literature and give ulterior information about HC prevalence and epidemiology in the preceding uncharted Italian territory.

Conflict of interest

The authors declare that there is no conflict of interest.

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