

Chapter 7

Correlation between age at neutering and age at onset of hyperadrenocorticism in ferrets

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Summary

Objective – To determine prevalence of hyperadrenocorticism in ferrets in The Netherlands and evaluate age, sex, and age at neutering in affected ferrets.

Design – Prevalence survey and retrospective study.

Animals – 50 ferrets with hyperadrenocorticism and 1,267 ferrets without hyperadrenocorticism.

Procedure – A questionnaire was sent to 1,400 members of a ferret-owners organization in The Netherlands; 492 (35%) owners returned the questionnaire, providing usable data on 1,274 ferrets. Seven of these ferrets developed hyperadrenocorticism during the survey period; medical records for these ferrets and 43 ferrets with confirmed hyperadrenocorticism were reviewed. Hyperadrenocorticism was confirmed by histologic examination of an excised adrenal gland (92% of ferrets) or clinical improvement after excision.

Results – Prevalence of hyperadrenocorticism in the survey population was 0.55%. Sex was not associated with prevalence of disease. Median time interval between neutering and diagnosis of hyperadrenocorticism was 3.5 years. A significant linear correlation between age at neutering and age at time of diagnosis was detected.

Conclusions and Clinical Relevance – Age at neutering may be associated with age at development of hyperadrenocorticism in ferrets.

Introduction

Hyperadrenocorticism is a common disease in pet ferrets.^{3,6,7,8,10} A review of this disease has been published;⁶ to our knowledge, reports have been based on observations made in the United States, where it is common practice to neuter ferrets at 6 weeks of age.⁸ Because hyperadrenocorticism is most often detected in neutered ferrets, it has been suggested that early neutering may contribute to the high prevalence of hyperadrenocorticism in ferrets.^{3,8} This theory is based on results of studies in certain strains of mice that develop nodular adrenocortical hyperplasia or adrenocortical tumors in 1 or both adrenal glands after neutering at an early age.^{2,4,9}

Because many ferrets in the United States are neutered at an early age⁸ and the population of sexually intact ferrets is relatively small, it is difficult to draw conclusions regarding a relation between hyperadrenocorticism and neutering at an early age. The objective of the study reported here was to determine the prevalence of hyperadrenocorticism in the Dutch ferret population, in which neutering at early age is not a common practice, and to determine influence of age, sex, and age at neutering for affected ferrets by review of medical records.

Materials and Methods

Owner survey

A short questionnaire was sent to 1,400 members of a Dutch ferret foundation (Stichting "De Fret") during April, May, and June 1997; the questionnaire solicited information on ferrets regarding age, sex, age at time of neutering, and whether members had ever owned a ferret with hyperadrenocorticism or presently owned a ferret with typical signs of hyperadrenocorticism, such as symmetric alopecia, swollen vulva (spayed females only), pruritus, and return of sexual behavior.

Retrospective study

Medical records of 50 ferrets with hyperadrenocorticism diagnosed at the Utrecht University Clinic for Companion Animals and several private veterinary practices in the Netherlands between January 1993 and September 1997 were reviewed; 7 of these ferrets were identified by results of the survey. Data regarding gross and microscopic pathologic findings, sex, age at neutering, age at time of diagnosis, and interval between neutering and time of diagnosis were recorded.

Statistical analyses

The Pearson coefficient of linear correlation was calculated to determine the relationship between age at neutering and age at diagnosis. Differences between groups were tested by use of χ^2 analysis or Student's *t* test. Prevalence of hyperadrenocorticism (percentage, confidence interval [CI]) in the survey population was calculated.¹¹ Differences were considered significant at $P < 0.05$.

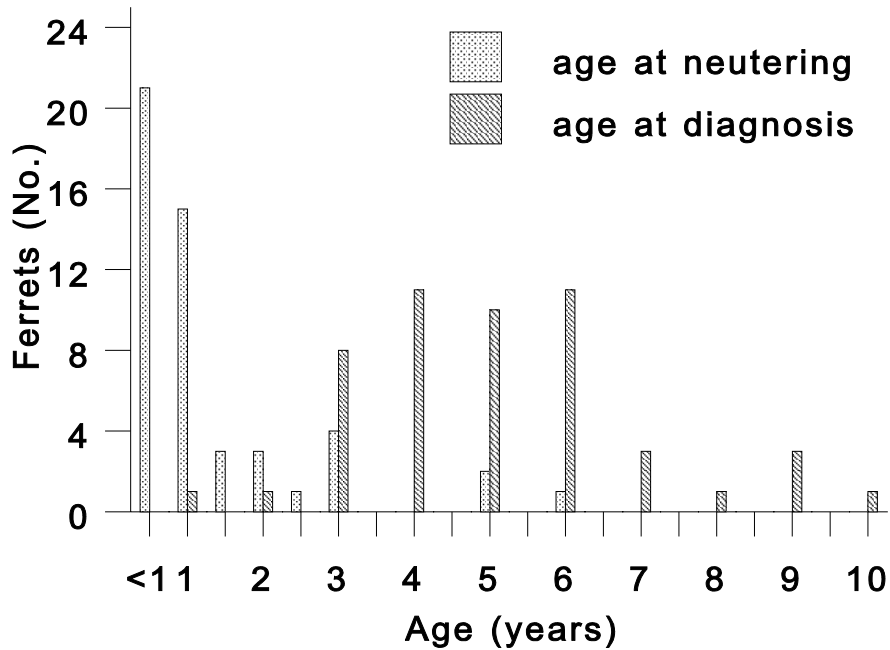


Figure 1. Age at neutering and age at diagnosis of hyperadrenocorticism in 50 ferrets.

Results

Owner survey

Of the 1,400 questionnaires sent, 492 (35%) were returned and provided data on 1,405 ferrets (782 male, 623 female) that had never had a diagnosis of hyperadrenocorticism. Data on age or age at neutering were lacking for 131 ferrets (88 male, 43 female); thus, data on 1,274 ferrets (694 male, 580 female) were used for analysis. Median age of this population was 3 years (mean \pm SD, 3.2 ± 1.7 years; range, 0.5 to 10 years). Median age of neutered ferrets was 3 years (mean, 3.4 ± 1.7 years; range, 0.5 to 10 years). Most ferrets (91% of males, 82% of females) had been neutered between 0.5 and 1.5 years old; median age at time of neutering was 1 year (mean, 0.98 ± 0.65 years; range, 0.5 to 6 years). In 108 ferrets, neutering had been performed after 1.5 years of age. Eighty-seven ferrets (25 male, 62 female) had not been neutered. Of these, 27 ferrets (11 male, 16 female) were > 1.5 years old. Median age of sexually intact ferrets was 1 year (mean, 1.6 ± 1.3 years; range, 0.5 to 6 years). Within the total survey population of 1,274 ferrets, 7 cases of hyperadrenocorticism were confirmed during the survey period by histologic examination of adrenal glands after adrenalectomy. Seven suspected cases of hyperadrenocorticism were also identified, but the owners did not allow further studies. Thus, prevalence of confirmed

Chapter 7

cases of hyperadrenocorticism in the survey population was 0.55% (95% confidence interval, 0.2 to 1.1%).

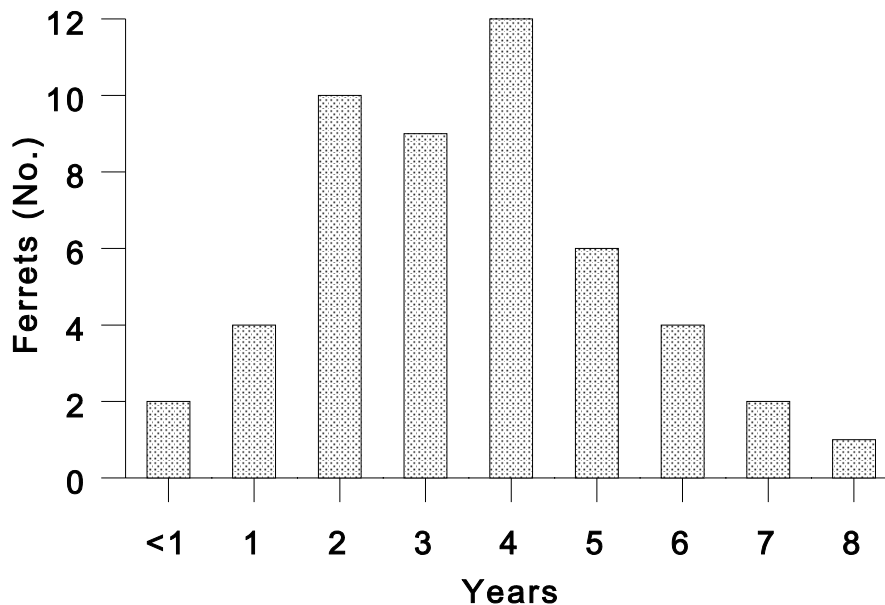


Figure 2. Interval between age at neutering and age at diagnosis of hyperadrenocorticism in 50 ferrets.

Retrospective study

For 46 of 50 ferrets with hyperadrenocorticism, the diagnosis was confirmed by histologic examination of surgical specimens obtained during unilateral adrenalectomy. Histologic diagnoses included intra- and extra-capsular hyperplasia, adenoma, and adenocarcinoma; distinctions between these differential diagnoses were difficult to determine, because adrenal tumors in ferrets seldom metastasize and microscopic characteristics overlap. For 4 ferrets, diagnosis was made on the basis of macroscopic appearance of adrenal glands and clinical improvement after adrenalectomy. All 50 ferrets (33 male, 17 female) with hyperadrenocorticism had been neutered. A significant difference in frequency distribution of sex between ferrets with hyperadrenocorticism and ferrets without hyperadrenocorticism was not detected. Median age at time of neutering was 1 year (mean, 1.4 ± 1.2 years; range, 0.5 to 6 years; Fig 1). Median age at diagnosis of hyperadrenocorticism was 5 years (mean, 5.1 ± 1.9 years; range, 1 to 10 years; Fig 1). Median interval between neutering and diagnosis of hyperadrenocorticism was 3.5 years (mean, 3.5 ± 1.8 years; range, 0.5 to 8 years; Fig 2). A significant linear correlation was found between age at neutering and age at diagnosis (Fig 3). Data on plasma estradiol and androgen concentrations were not available.

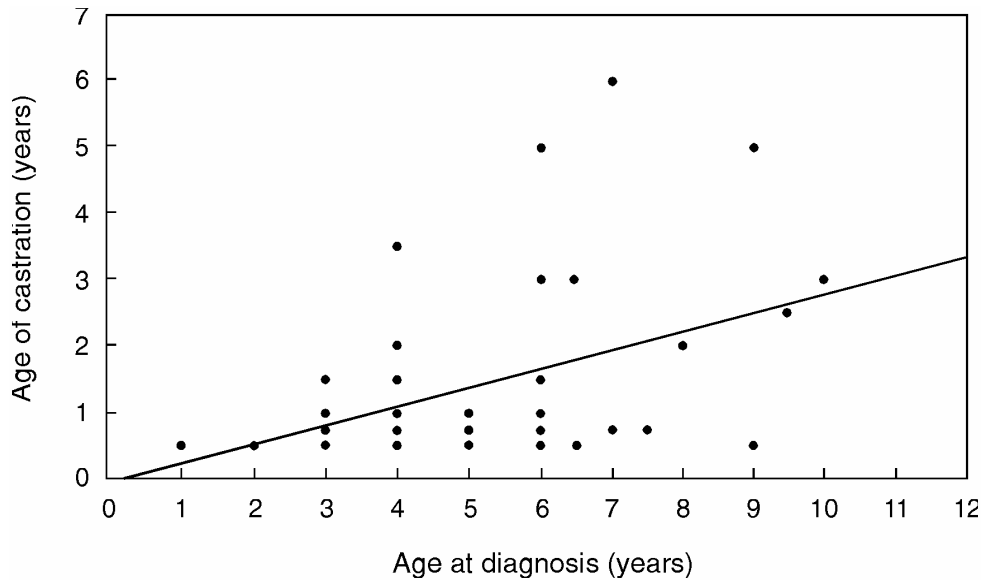


Figure 3. Scatterplot of age at neutering and age at diagnosis of hyperadrenocorticism in 50 ferrets ($y = -0.064 + 0.285x$; $r = 0.437$; $P < 0.01$)

Discussion

To our knowledge, this is the first report of the prevalence of hyperadrenocorticism in ferrets. Weiss and Scott¹⁰ reported that 20 to 25% of ferrets examined in their practice had hyperadrenocorticism, but this may not be a reliable indication of prevalence because it was based on a selected population. In our study of a Dutch ferret population, prevalence was estimated to be 0.55% (95% CI, 0.2 to 1.1%); 7 other ferrets were reported with typical clinical signs, but owners refused further diagnostic efforts. The fact that ferrets with hyperadrenocorticism seldom have increased plasma cortisol concentrations⁷ prevents useful comparisons between hyperadrenocorticism in ferrets and hyperadrenocorticism in dogs, cats, or humans. Nevertheless, a prevalence of 0.55% must be considered high.

A significant correlation was found between age at neutering and age at diagnosis, suggesting that age at neutering may influence age of onset of this condition; however, the disease has also been reported in 7 sexually intact ferrets.^{7,8,10} Many more cases in sexually intact ferrets may have gone unnoticed, because sexual behavior – a common clinical sign of the disease – may not be regarded as abnormal in a sexually intact ferret, whereas it is considered abnormal in a neutered ferret and may cause the owner to seek veterinary assistance.

Results reported from some institutions indicate almost twice as many female as male ferrets with adrenal tumors, but selection bias, rather than actual difference in prevalence,

Chapter 7

was given as a possible explanation.⁶ In the population described by Weiss and Scott,¹⁰ the distribution between sexes was equal. Although two-thirds of the ferrets with hyperadrenocorticism in the study reported here were male, differences in the proportions of males and females among ferrets with and without hyperadrenocorticism were not significant; sex did not affect prevalence of the disease.

In our study, mean age of ferrets with hyperadrenocorticism was 5.1 ± 1.9 years; significantly older than affected ferrets (mean age, 3.4 ± 1.4 years; $n = 50$) reported by Rosenthal *et al.*⁸ In the Netherlands, ferrets are neutered at 0.98 ± 0.65 years of age; American ferrets are commonly neutered at 4 to 6 weeks of age.⁸ The interval between age at neutering and age at diagnosis in the Dutch ferret population (3.5 ± 1.8 years) was, however, similar to that in the population studied by Rosenthal *et al.* (3.3 ± 1.4 years),⁸ assuming that those ferrets were neutered at 6 weeks of age. Although a significant correlation between age at neutering and age at development of hyperadrenocorticism is apparent, an explanation for this relationship has yet to be found. It has been speculated that, after neutering, the adrenal cortices are persistently stimulated by luteinizing hormone (LH) and follicle-stimulating hormone (FSH) as a result of the loss of negative gonadal feedback on hypothalamic gonadotropin releasing hormone (GnRH), and this results in adrenocortical hyperplasia or tumorigenesis^{3,8}; Donovan and ter Haar¹ detected increased plasma concentrations of LH and FSH in spayed female ferrets. Luteinizing hormone receptors have been found in the adrenal glands of humans,⁵ suggesting that increased LH concentrations in plasma could be a triggering factor for development of adrenal tumors. The successful use of the GnRH agonist leuprolide for medical control of hyperadrenocorticism strengthens the hypothesis that neutering plays a role in the development of hyperadrenocorticism in ferrets (Johnson-Delaney CA, personal communication, 1999).

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