Ultrasonographic Visualization of the Adrenal Glands of Healthy Ferrets and Ferrets With Hyperadrenocorticism

A protocol was developed to compare the ultrasonographic characteristics of the adrenal glands of 21 healthy ferrets and 37 ferrets with hyperadrenocorticism. By using specific landmarks, the adrenal glands were imaged in 97% of the cases. The adrenal glands of ferrets with hyperadrenocorticism had a significantly increased thickness, with changes in shape, structure, and echogenicity compared to the adrenal glands of healthy ferrets. Based on the findings of the study, adrenal glands may be classified as abnormal when they have a rounded appearance, increased size of the cranial/caudal pole (thickness >3.9 mm), a heterogeneous structure, increased echogenicity, and/or signs of mineralization.

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Introduction

Hyperadrenocorticism is a common disease in ferrets, which differs from the disease seen in humans, dogs, and cats. In the latter species, a high concentration of cortisol is responsible for the clinical signs, while in ferrets signs are caused by high concentrations of sex-related steroids.[1-4] Over 70% of the cases of hyperadrenocorticism in humans, dogs, and cats are caused by a pituitary tumor; in ferrets, the primary cause of the disease is always a uni- or bilateral abnormality of the adrenal gland.[1-7] The most prominent clinical signs of hyperadrenocorticism in ferrets are symmetrical alopecia, vulvar swelling in spayed female ferrets (jills), nonparasitic or nonfungal-related pruritus, stranguria in castrated male ferrets (hobs), and the return of sexual behavior despite ovariectomy or castration.[8-10]

It has been reported that the diagnosis of hyperadrenocorticism in ferrets can be based on clinical signs, plasma hormone concentrations (i.e., androstenedione, 17α-hydroxy-progesterone, dehydroepiandrosterone sulfate, estradiol), an elevated urinary corticoid to creatinine ratio, and an enlarged adrenal gland seen during ultrasonography.[1,2,4,9,11-18] Measurement of hormone concentrations, however, does not allow differentiation between hyperadrenocorticism and functional ovarian remnant tissue, nor does it provide information as to whether the left or right adrenal gland is affected.[2,4,11,12] Ultrasonography has been used to identify affected adrenal glands and to assess their size, shape, structure, and possible vascular invasion.[1,9,13-18] In addition, abnormalities of other abdominal organs, such as remnant ovarian tissue, may be found with ultrasonography.

Since the introduction of medical treatment of hyperadrenocorticism with the gonadotropin-releasing hormone (GnRH) agonist, leuprolide acetate,[a] adrenalectomies are less frequently performed, which seemingly makes the need for localizing affected adrenal gland(s) less important. By administering a GnRH agonist, the production and release of gonadotropins are suppressed, resulting in a decreased production of adrenocortical hormones and a reduction of the clinical signs in affected

ferrets.[12] In ferrets and in at least one woman with hyperadrenocorticism treated with leuprolide acetate, the affected adrenal gland did not decrease in size and actually increased in size after the treatment.[12,19] The actual effect of leuprolide acetate on altered adrenal glands in ferrets is poorly understood, so evaluation of the adrenal glands via ultrasonography during leuprolide treatment would be useful.

The ultrasonographic size and appearance of adrenal lesions of ferrets with hyperadrenocorticism have been described.[1,15-17] These reports did not describe the exact method of visualization of the adrenal glands, and the accuracy with which adrenal glands were identified varied considerably (50% to 100%).[1,9,15-18] The lower detection rates have led some authors to suggest that ultrasonography may be of little value in diagnosing hyperadrenocorticism in ferrets.[3] The purposes of the present study were to assess a protocol for visualizing adrenal glands in ferrets using ultrasonography and to document the size, shape, and structure of the adrenal glands in both healthy ferrets and ferrets with hyperadrenocorticism.

Materials and Methods

Selection of Cases

The medical records of ferrets that were presented to the Division of Avian and Exotic Animal Medicine of the Faculty of Veterinary Medicine in Utrecht, the Netherlands, with signs of hyperadrenocorticism between April 1999 and April 2005 were reviewed. Only ferrets with at least one clinical sign of hyperadrenocorticism (e.g., symmetrical alopecia, nonparasitic or nonfungal-related pruritus, return of sexual behavior despite ovariectomy or castration, vulvar swelling in jills, stranguria in hobs) that experienced resolution of their clinical sign(s) with therapy (i.e., adrenalectomy, leuprolide or deslorelin[b] administration) were included in the study. Thirty-seven ferrets met the criteria for inclusion. Signalment (i.e., age, gender) and clinical signs for these ferrets were recorded.

For comparison, the adrenal glands of 21 healthy research ferrets (based on a young age [<2 years], normal history and physical examination findings) were examined ultrasonographically, with the approval of the Ethics Committee of the Faculty of Veterinary Medicine, Utrecht, the Netherlands.[20] These ferrets were individually housed at the Division of Avian and Exotic Animal Medicine in outdoor, suspended cages with a closed sleeping area. Water and ferret pellets[c] were available *ad libitum*.

Anatomy

The adrenal glands are located craniomedial to the cranial pole of the kidneys. The left adrenal gland is located ventrolateral to the aorta at the level of and/or immediately caudal to the origin of the cranial mesenteric artery. The right adrenal gland is located more cranial than the left, and it is attached to the dorsal and dorsolateral surface of the caudal vena cava at the level of and/or immediately cranial to the origin of the cranial mesenteric artery, and it lies adjacent to the caudomedial aspect of the caudate process of the caudate liver lobe.[17,21-23]

The ultrasonographic craniocaudal (length) and ventrodorsal (thickness) dimensions of normal ferret adrenal glands are 5.4 to 9.8 mm and 2.3 to 3.6 mm, respectively, for the left gland and 5.8 to 10.5 mm and 2.2 to 3.8 mm, respectively, for the right gland.[17,18] The normal shape of the adrenal gland varies from oblong to ovoid, slightly bilobed, or rectangular.[1,17,18]

Ultrasonography Protocol

Food was withheld from all ferrets for at least 4 hours prior to ultrasonography. Anesthesia was induced by mask inhalation of 4% isoflurane[d] in oxygen and was maintained with 2% isoflurane. Ultrasonography was performed with a high-definition ultrasound system[e] equipped with a 38-mm long, 10- to 5-MHz, broadband, linear-array transducer (lateral resolution of 1.1 mm and axial resolution of 0.9 mm at a depth of 2 cm). The ferrets were placed in dorsal recumbency, and the transducer was gently placed on the abdominal wall to avoid compression or distortion of the abdominal organs and/or blood vessels.

Scanning along a longitudinal plane through the ventral abdominal wall, the left kidney was identified. With the cranial edge of the kidney approximately in the center of the image, the transducer was angled, orienting the soundbeam gradually from a vertical to a more horizontal plane. The ultrasonic beam traversed the aorta from dorsal to ventral and then across the celiac and cranial mesenteric arteries. The left adrenal gland was then located. When necessary, the transducer was slightly rotated to obtain a maximal longitudinal image of the left adrenal gland [Figure 1]. From this position, the transducer was rotated 90˚ to obtain transverse images.

Scanning along a longitudinal plane to the right of the midline, the right adrenal gland was found dorsal to the caudal vena cava, just where it enters the liver. When this technique was not immediately successful, the liver was examined in a transverse direction, and the aorta, caudal vena cava, and portal vein were identified. By slightly angling the transducer in a craniocaudal direction and moving the transducer gradually in a caudal direction along the caudal vena cava, and using the liver as an acoustic window as much as possible, the right adrenal gland was then located. The caudal pole of the right adrenal gland may be more lateral than dorsal to the caudal vena cava.

When this technique failed, a right lateral approach was used, with the animal in left lateral recumbency. Transverse and longitudinal scans through the last intercostal spaces and the right flank were used to identify the aorta and caudal vena cava. In the area where the caudal vena cava enters the liver, at the level of and/or immediately cranial to the origin of the cranial mesenteric artery, the right adrenal gland lies dorsal to the caudal vena cava. Once the right adrenal gland was identified using any of these three approaches (i.e., midline longitudinal, midline traverse, right lateral longitudinal), the transducer was rotated slightly until a longitudinal image of the right adrenal gland was obtained [Figure 2A]. From this position, the transducer

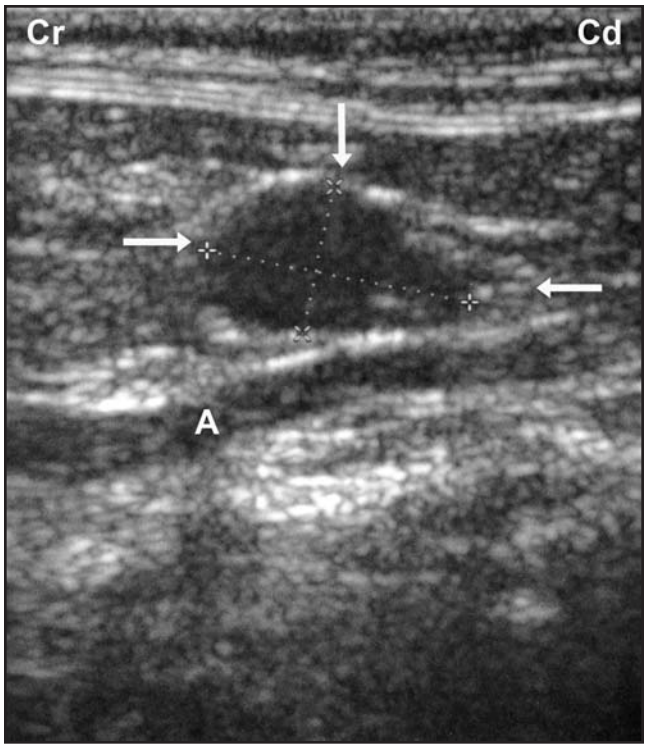
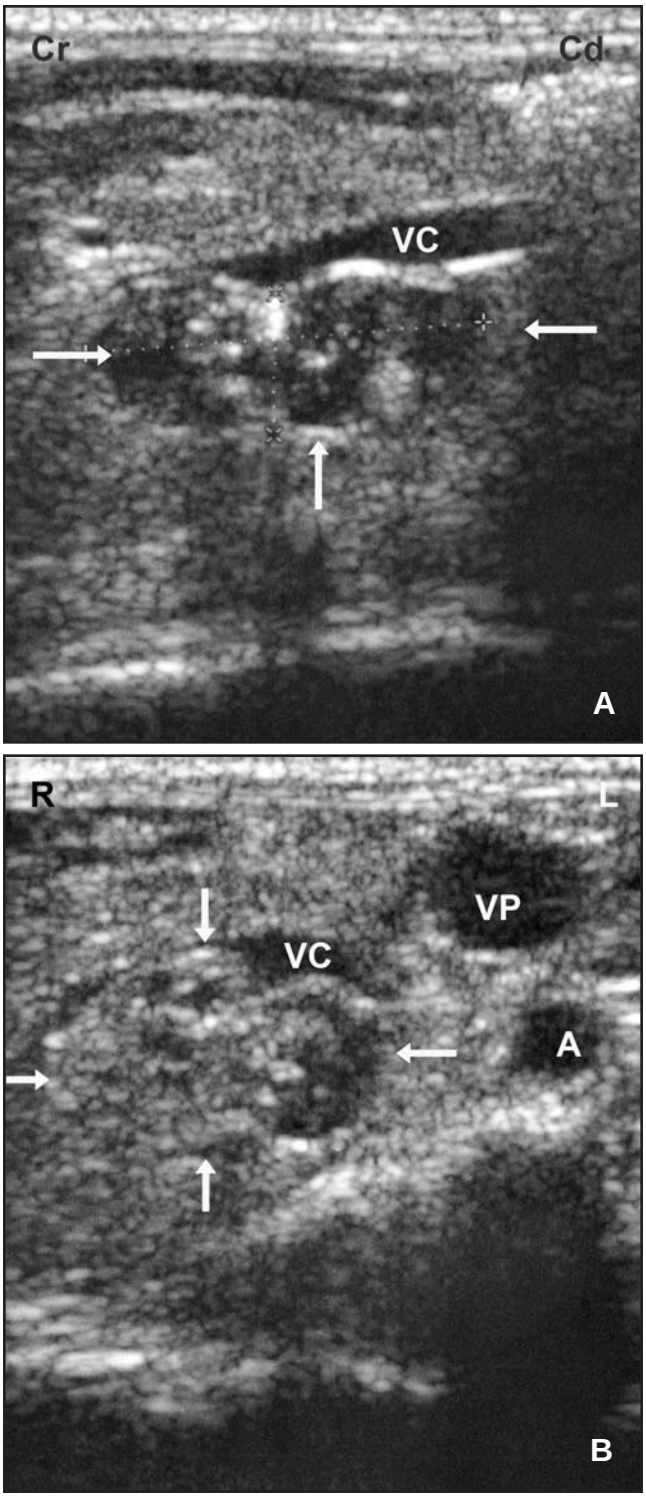


Figure 1—A longitudinal sonogram of a left adrenal gland (between the arrows) in a 3.5-year-old, spayed female ferret with hyperadrenocorticism. The cranial pole is enlarged. Adrenal length is 10.4 mm, and thickness is 6.4 mm. Histopathological diagnosis was adrenocortical hyperplasia. Note the location of the adrenal gland ventrolateral to the aorta (A). The top of the image is ventral, Cr=cranial, Cd=caudal.



Figures 2A, 2B—Longitudinal **(A)** and transverse **(B)** sonograms of the right adrenal gland (between the arrows) in a 6.5-year-old, castrated male ferret with hyperadrenocorticism. The adrenal gland is hyperechoic, heterogeneous, and contains mineralizations (hyperechoic spots). The adrenal gland length is 15.6 mm, and thickness is 5.5 mm. The right adrenal gland is located dorsolateral to the vena cava (VC). The top of the image is ventral, A=aorta, VP=vena porta, R=right, L=left, Cr=cranial, Cd=caudal.

was rotated 90˚ to obtain transverse images [Figure 2B]. During the ultrasonographic examination, color-flow Doppler was used to assess blood flow in the aorta, celiac and cranial mesenteric arteries, and caudal vena cava. These vessels were used as landmarks.

From the ultrasound images, the craniocaudal (length) and ventrodorsal (thickness) dimensions of the adrenal glands were measured using cursors and the ultrasound system's software. The shape, structure (e.g., homogeneous, heterogeneous, cystic, mineralized), and overall echogenicity (as compared to the surrounding fat) were assessed visually. Differentiation between normal and abnormal adrenal glands in the ferrets with hyperadrenocorticism was made subjectively on the basis of the size, shape, and structure. Adrenal glands were classified as being abnormal when they were increased in size (as compared to the contralateral gland and/or the reference values for healthy ferrets), had an abnormal shape (e.g., rounded, asymmetry of the cranial and caudal pole), or had an altered structure.[17,18]

Statistical Analysis

A Mann-Whitney U test[f] was used to determine significant differences between the sizes of the adrenal glands in

healthy ferrets and the sizes of both normal and affected adrenal glands in ferrets with hyperadrenocorticism. Values of $P<0.01$ were considered statistically significant.

Reference ranges for adrenal gland size in the healthy ferrets and the normal adrenal glands in the ferrets with hyperadrenocorticism were calculated using the formula: mean ± ($t \times$ standard deviation [SD]).[24,25] The positive and negative predictive values of these results in the healthy ferrets were also assessed. The adrenal gland sizes of the affected ferrets were log transformed (to base *e*) to meet the assumption of normality; then, using the transformed data, a reference range was calculated, which was converted back to the original scale by taking the antilogarithm.[25]

Results

Clinical Data

Thirty-seven privately owned ferrets with hyperadrenocorticism were included in the study. They ranged in age from 2 to 7.5 years (mean 5.0±1.2 years). The ferrets consisted of 16 castrated males and 21 spayed females (male to female ratio=0.76). The most common presenting clinical signs were symmetrical alopecia (n=34), pruritus (n=11), vulvar swelling (n=12 females), fatigue (n=8), weight loss (n=7), the return of sexual behavior despite ovariectomy or castration (n=6), and stranguria (n=2 males). Twelve ferrets were treated by adrenalectomy, 18 ferrets received leuprolide acetate injections, and seven ferrets were treated with a 9.5-mg GnRH implant.

Twenty-one research ferrets were used as normal controls, and they ranged in age from 8 to 23 months. The normal ferrets consisted of 10 females, eight males, and three spayed females. All the research ferrets were kept for at least 4 years after completing the study, and none developed clinical signs of hyperadrenocorticism.

Adrenal Glands of Healthy Ferrets

In the 21 normal ferrets, 41 adrenal glands were identified (accuracy 98%). One right adrenal gland could not be identified ultrasonographically. The adrenal glands were oblong to oval in shape, uniformly structured, and hypoechoic to the surrounding fat. The mean dimensions of the left adrenal glands were 6.1±1.0 mm (range 4.5 to 8.3 mm; reference range 4.0 to 8.1 mm) for length and 2.9±0.5 mm (range 1.8 to 3.7 mm; reference range 1.8 to 3.9 mm) for thickness. The positive and negative predictive values of these dimensions were 93% and 57%, respectively, for length and 100% and 78%, respectively, for thickness. The mean dimensions of the right adrenal glands were 7.8±1.4 mm (range 4.6 to 9.8 mm; reference range 4.9 to 10.6 mm) for length and 2.5±0.6 mm (range 1.4 to 3.6 mm; reference range 1.3 to 3.7 mm) for thickness. The positive and negative predictive values of these dimensions were 100% and 56%, respectively, for length and 100% and 77%, respectively, for thickness [see Table].

Adrenal Glands of Affected Ferrets

Both adrenal glands were identified by ultrasonography in 35 of the 37 affected ferrets (accuracy 97%). In two ferrets, the right adrenal gland could not be identified. Based on the dimensions, structure, and echogenicity of the 72 adrenal glands that were identified, 48 were classified as abnormal (28 left, 20 right), and 24 were classified as normal. Bilateral lesions were found in 11 (30%) ferrets. The mean dimensions of the 28 abnormal left adrenal glands were 9.2±3.2 mm (range 5.0 to 19.5 mm; reference range 4.6 to 16.6 mm) for length and 6.3±3.0 mm (range 2.4 to 15.1 mm; reference range 2.4 to 13.8 mm) for thickness. The dimensions of 19 abnormal right adrenal glands were 8.5±2.5 mm (range 4.6 to 15.2 mm; reference range 4.5 to 14.9 mm) for length and 5.2±3.3 mm (range 2.2 to 17.6 mm; reference range 1.7 to 12.8 mm) for thickness. The abnormal adrenal glands in the ferrets with hyperadrenocorticism had a significant increase ($P<0.01$) in the length of the left adrenal gland and in the thickness of both adrenal glands [see Table] when compared to the dimensions of the normal adrenal glands.

All 28 abnormal left adrenal glands had an altered shape; 25 (89%) had a rounded appearance, and four (14%) had a large or rounded cranial pole. Seven (25%) of the 28 left adrenal glands had a heterogeneous structure, and six (21%) had increased echogenicity compared to the surrounding fat. The other 22 left adrenal glands had normal echogenicity (hypoechoic to the surrounding fat). Of the 20 abnormal right adrenal glands, 18 had an altered shape, 10 (56%) had a rounded appearance, four (22%) had a large or rounded cranial pole, and one (6%) had a large or rounded caudal pole. In seven (35%) of the 20 right adrenal glands, a heterogeneous structure (pattern) was found, and eight (40%) had increased echogenicity. In two of these eight adrenal glands, mineralization was detected. The other 12 right adrenal glands had normal echogenicity.

Histology was performed in the 12 affected adrenal glands that were surgically removed (all left adrenal glands). The histopathological diagnoses included cortical hyperplasia (n=5), adenoma (n=2), adenocarcinoma (n=2), carcinoma (n=1), and an unspecified adrenal tumor (n=2). There was no significant difference in size between the surgically removed and nonoperated abnormal adrenal glands (Mann-Whitney U test, $P=0.15$).

Twenty-four adrenal glands of ferrets with hyperadrenocorticism were classified as being normal (nine left, 15 right). The mean dimensions of the left adrenal glands were 6.3±0.9 mm (range 5.1 to 7.7 mm; reference range 4.2 to 8.4 mm) for length and 2.5±0.6 mm (range 1.4 to 3.4 mm; reference range 1.2 to 3.8 mm) for thickness. The mean dimensions of the right adrenal glands were 6.0±1.7 mm (range 3.7 to 9.2 mm; reference range 2.3 to 9.6 mm) for length and 2.1±0.6 mm (range 1.3 to 3.7 mm; reference range 0.8 to 3.5 mm) for thickness [see Table]. There were no statistical differences between the dimensions of the normal adrenal glands of affected ferrets and those of normal ferrets with regard to length of the left adrenal gland ($P=0.48$), thickness of the left adrenal gland ($P=0.06$), and thickness of the right adrenal gland ($P=0.07$). The length of the right adrenal gland of affected ferrets was statistically smaller ($P=0.004$) than that of the normal ferrets.

Table

Ultrasonographic Dimensions of the Adrenal Glands of Healthy Ferrets and Ferrets With Hyperadrenocorticism

	Left Adrenal Gland				Right Adrenal Gland			
	Length (mm)		Thickness (mm)		Length (mm)		Thickness (mm)	
Study Subjects	Mean ± SD*	Reference Range	Mean ± SD	Reference Range	Mean ± SD	Reference Range	Mean ± SD	Reference Range
Healthy ferrets (n=21)†	6.1±1.0	4.0-8.1	2.9±0.5	1.8-3.9	7.8±1.4	4.9-10.6	2.5±0.6	1.3-3.7
Ferrets with hyperadrenocorticism (n=37)‡								
Abnormal glands (left=28, right=20)§	9.2±3.2¶	4.6-16.6¶	6.3±3.0¶	2.4-13.8¶	8.5±2.5	4.5-14.9	5.2±3.3¶	1.7-12.8¶
Normal glands (left=9, right=15)\	6.3±0.9	4.2-8.4	2.5±0.6	1.2-3.8	6.0±1.7#	2.3-9.6#	2.1±0.6	0.8-3.5

* SD=standard deviation
† n=number of ferrets; one right adrenal gland was not identified, and length could not be measured in one right adrenal gland
‡ n=number of ferrets; two right adrenal glands were not identified
§ Length could not be measured in one right adrenal gland, and thickness could not be measured in one right adrenal gland
\ Length could not be measured in one right adrenal gland
¶ Values were significantly ($P<0.01$) larger compared to values for healthy ferrets, using the Mann-Whitney U test
# Value was significantly smaller ($P=0.004$) compared to values for healthy ferrets, using the Mann-Whitney U test

Discussion

The ultrasonographic protocol used in this study allowed identification of 98% of the adrenal glands in the healthy ferrets and 97% of the adrenal glands in the affected ferrets, which was higher than several previous reports.[1,9,15-18] Detection rates may have been lower in earlier reports because of the presence of large lymph nodes in the abdomen of ferrets. These lymph nodes have a round or oval shape, are usually hypoechoic compared to surrounding fat, and resemble adrenal glands.[26] By using the anatomical landmarks (e.g., the right adrenal gland is attached to the dorsolateral surface of the caudal vena cava; the left adrenal gland is located ventrolateral to the aorta, just caudal to the origin of the cranial mesenteric artery), differentiation between lymph nodes and adrenal glands is relatively easy.

In the study reported here, abnormal adrenal glands in the ferrets with hyperadrenocorticism had a significant increase in thickness. A greater length was found in abnormal left adrenal glands, but not in abnormal right adrenal glands, which may be explained by the fact that the cranial pole of the right adrenal gland lies dorsal to the caudal vena cava, and the caudal pole is usually dorsolateral or lateral to the caudal vena cava, making it difficult to obtain a longitudinal image that contains the whole adrenal gland.[14,17,18,23] Similar to the findings in other studies, the abnormal adrenal glands were fairly rounded in shape or had a large cranial and/or caudal pole.[1,14-16] It is hypothesized that early in the disease, thickness increases rather than the length, which results in a round gland or increased size of one pole. Eventually, the entire gland is affected and the internal architecture is disrupted.[17]

The adrenal gland size in the 21 healthy ferrets was in accordance with previous studies.[17,18] The size of the normal adrenal glands in the healthy animals resembled the size of the normal adrenal glands of the affected ferrets, except for the length of the right adrenal gland. Again, difficulties in accurately measuring the length of right adrenal glands may have affected these results.

The control group consisted of a large number of intact ferrets (n=18), unlike the group of affected ferrets (none of which were intact). Since hyperadrenocorticism is predominantly found in neutered ferrets, it was believed that the adrenal size in intact ferrets was a correct representation of normal size.[1-4]

Adrenal neoplasms can also be identified ultrasonographically by a change in adrenal shape and structure.[17] In 14 (29%) of the 48 abnormal adrenal glands, the structure was heterogeneous, and 14 (29%) had increased echogenicity. In previous studies, echogenicity of abnormal adrenal glands has been described as mixed or hyperechoic, but the ultrasonographic technique used and the number of affected glands imaged were not reported.[1,13,14,16,18] An affected adrenal gland can also have a normal structure and echogenicity.[1,14,18] In the current study, 28 (58%) of 48 abnormal adrenal glands had a normal structure and were hypoechoic; however, they were all increased in size and/or had a rounded appearance. Only two (4%) of the 48 abnormal adrenal glands contained mineralized areas, similar to previous reports in which mineralization is rarely described.[1,9,13,15-18]

The lesions found in this study involved 28 left and 20 right adrenal glands, which contradicted the historical impression that adrenal gland lesions mostly affect the left adrenal gland.[16] Bilateral lesions were found in 11 (30%) ferrets; this percentage was greater than that previously described (16% to 19%).[1,9,10] This latter difference may be explained by the subjective element involved in the differentiation of normal versus abnormal adrenal glands, which can lead to the under-interpretation of minor changes in an adrenal gland after obvious abnormalities have been found in the contralateral adrenal gland. The findings of equal distribution of adrenal lesions of the left and right adrenal glands and a high percentage of bilateral lesions are in accordance with the suggested pathogenesis of hyperadrenocorticism, which is overstimulation of the adrenal glands by luteinizing hormone following neutering.[9,27]

Normal adrenal glands in the ferret are oblong to oval in shape, uniformly structured, and hypoechoic to the surrounding fat. Increased echogenicity was found during ultrasonographic examination in two of the adrenal glands in the healthy ferrets (both intact males), possibly because they contained more fat. These two male ferrets had the highest body weights of all the healthy ferrets examined, and they may have stored more fat in their adrenal glands.

Since ultrasonography is relatively inexpensive and noninvasive, it is the most practical method for imaging the adrenal glands. Ultrasonography can also detect the presence of an intact female genital tract or an ovarian remnant (the two most important differential diagnoses for hyperadrenocorticism in young [<2 years of age], female ferrets), and it may be used to monitor changes in adrenal gland size and structure during the course of hormonal therapy.[28] Ultrasonography permits evaluation of all abdominal organs for secondary effects, may identify an adrenal gland tumor, and also facilitates percutaneous-guided biopsy.[23]

Based on the results of this study, adrenal glands should be classified as abnormal when they have a rounded appearance, have an enlarged cranial and/or caudal pole (thickness >3.9 mm), a heterogeneous structure, increased echogenicity, and/or contain mineralizations. By using the specific landmarks described in the protocol, the accuracy of an ultrasonographic examination increased to such extent that almost all adrenal glands were imaged. For each of the 12 ferrets in the present study in which the affected adrenal gland was removed surgically, the clinical signs of hyperadrenocorticism resolved within 1 month following surgery, indicating that the adrenal gland considered normal on ultrasonographic examination was functionally normal. A normal shape, structure, and echogenicity of a ferret's adrenal gland, however, does not rule out a functional adrenal lesion.

Conclusion

Ultrasonography was very accurate in identifying abnormal adrenal glands in 37 ferrets with signs of hyperadrenocorticism, after specific landmarks were identified. Adrenal glands were classified as abnormal when they had a rounded appearance, an enlarged cranial and/or caudal pole, a heterogeneous structure, increased echogenicity, and/or contained mineralization.

[a] Lucrin; Abbott Animal Health, Hoofddorp, The Netherlands
[b] Suprelorin; Peptech Animal Health Pty Ltd, North Ryde, Australia
[c] FerRet; Hope Farms, Woerden, The Netherlands
[d] IsoFlo; Abbott Animal Health, Hoofddorp, The Netherlands
[e] ATL HDI 3000; Philips Medical Systems, Eindhoven, The Netherlands
[f] SPSS; SPSS Inc., Chicago, IL 60606

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