Diabetes mellitus and hypercortisolism in a cat

Diabetes mellitus en hypercortisolisme bij een kat

[1]E. Odent, [1]S. Marynissen, [2]E. Stock, [1]S. Vandenabeele, [1]I. Van de Maele, [1]S. Daminet

[1]Department of Small Animals
[2]Department of Medical Imaging of Domestic Animals and Orthopedics of Small Animals
Faculty of Veterinary Medicine, Ghent University
Salisburylaan 133, B-9820 Merelbeke, Belgium

evelien.odent@ugent.be

ABSTRACT

A fourteen-year-old Persian cat was referred because of poorly controlled diabetes mellitus despite insulin and dietary treatment. Clinical signs were severe polydipsia/polyuria (pupd), poor hair coat quality, stomatitis and hind limb weakness. At the time of initial presentation, he was treated with glargine insulin (0,75 IU/kg BID). A low dose dexamethasone suppression test (LDDST) revealed hypercortisolism (HC). The cat was additionally treated with trilostane, and remission of diabetes mellitus was obtained one year later.

This case illustrates the importance of diagnosing an underlying cause of poorly controlled diabetes mellitus. Although hypercortisolism is rare in cats, it is important to consider the disease in these cases. The hypercortisolism in this cat was efficiently managed with trilostane, resulting in a good quality of life.

SAMENVATTING

Een veertien jaar oude Perzische kat werd doorverwezen vanwege slecht gereguleerde diabetes mellitus ondanks insulinebehandeling en een aangepast dieet. De kat vertoonde uitgesproken polyurie/polydipsie, een slechte vachtkwaliteit, stomatitis en zwakte op de achterhand. Op dat moment werd hij behandeld met glargine insuline (0,75 IE/kg BID). Met behulp van een lage-dosis-dexamethasone-suppressie-test (LDDST) werd hypercortisolisme (HC) gediagnostiseerd. De kat werd bijkomend behandeld met trilostane en één jaar later werd remissie van diabetes mellitus bekomen.

Deze casuïstiek illustreert het belang van de diagnose van een onderliggende oorzaak van slecht gereguleerde diabetes mellitus. Ook al is hypercortisolisme zeldzaam bij katten, het is belangrijk de ziekte bij deze gevallen in de differentiaaldiagnose op te nemen. Hypercortisolisme werd bij deze patiënt behandeld met trilostane, resulterend in een goede levenskwaliteit.

INTRODUCTION

Diabetes mellitus (DM) is a common endocrine disease in cats. It is defined as a relative or absolute insulin deficiency that causes persistent hyperglycemia. The classification of DM is based on the mechanism of insulin deficiency. In analogy with human classification, it can be divided in type 1, type 2 and 'other specific types' of diabetes. Approximately 80 to 95 % of diabetic cats are thought to have type 2 diabetes mellitus (Rand, 2013; Gostelow et al., 2014).

Type 2 initiates with a relative deficiency of insulin that later becomes an absolute deficiency. Factors that contribute to insulin resistance are genotype, obesity, physical inactivity and diet. The β-cells try to compensate by secreting more insulin. The chronic high demand for insulin leads to β-cell failure and loss through apoptosis causing insulin deficiency (Niessen et al., 2013; Rand, 2013).

The management of diabetic cats can be challenging. In these cases, the etiopathogenesis of DM may not be type 2 but an underlying disease. This type is categorized as 'other specific types of diabetes'. Some of these diseases, such as pancreatitis and pancreatic

Figure 1. Poor hair coat quality and discoloration.

Figure 2. Alopecia of the ventral abdomen.

neoplasia, destroy β-cells. Other diseases, such as hypersomatotropism and hypercortisolism, induce diabetes by producing an excess of growth hormone and cortisol, respectively. These hormones cause insulin resistance (Rand, 2013; Niessen et al., 2013). Currently, hypersomatotropism is thought to be the underlying disease in feline DM in 25 to 30% of cases (Rand and Gottlieb, 2017).

Insulin resistance can be an important component of the pathogenesis of diabetes mellitus secondary to an underlying disease. Resolution of peripheral insulin resistance together with good glycemic control may result in remission of feline diabetes (Scott-Moncrieff, 2010).

Contrary to dogs, hypercortisolism (HC) is rare in cats. The main differences and similarities in HC between dogs and cats are summarized in Table 1. In most cases (85 %), HC is caused by a tumor of the pituitary gland (pituitary-dependent HC). The elevated secretion of adrenocorticotropic hormone (ACTH) causes hyperplasia of both adrenal glands and an increase in production of cortisol. In approximately 15 % of HC in cats, it is caused by functional adrenal tumors that autonomously secrete cortisol. Fifty percent are malignant adenocarcinomas (Bhatti and Daminet, 2004; Chiaramonte and Greco, 2007; Feldman, 2014).

In this article, a cat with DM and HC is described. Medical treatment of HC in cats with trilostane is further addressed.

CASE REPORT

A fourteen-year-old, male, castrated Persian cat of 5.25 kg was presented at the Small Animal Clinic, Faculty of Veterinary Medicine (Ghent University) for poorly controlled DM (day 0). Four months before, diabetes mellitus had been diagnosed and therapy with insulin (Caninsulin®, MSD Animal Health, Brussels, Belgium) was initiated. The insulin dose was gradually increased to 6 IU BID (1.14 IU/kg) based on blood glucose curves, performed at home (HMBG), still showing poorly controlled DM. Baseline data (complete blood count, biochemistry profile, electrolytes) were obtained by the referring veterinarian at the time of diagnosis. Values were within normal limits. IGF-1, measured by the referring veterinarian after six weeks of insulin treatment, was 21.4 nmol/L (163 µg/L) (1.4 (10.7) – 53.8 (411)). Three months after diagnosis, therapy was changed to glargine (Lantus®, Sanofi-Aventis, Frankfurt am Main, Germany). At the time of presentation at the Small Animal Clinic, the cat received 4 IU BID (0.75 IU/kg), without significant improvement.

The patient presented with persistent pupd, poor hair coat and discoloration and hind limbs weakness (Figures 1 and 2). The body condition score was 6/9 and the cat was fed a diabetic diet ad libitum (Royal Canin Diabetic®).

On physical examination, stomatitis, halitosis and mild hepatomegaly were noticed. To search for underlying diseases and assess the adrenal glands, an abdominal ultrasound was performed and revealed mild hepatomegaly with a homogenous hyperechoic parenchyma, suggestive of lipidosis. Both adrenal glands had a normal shape, the left gland was normal in size (4.1 mm), whereas the right gland was mildly enlarged (5.6 mm) (Figure 3). The mildly enlarged right adrenal gland could be an incidental finding, i.e. anatomical variation, measurement variability. However hyperplasia secondary to pituitary disease (PDH or acromegaly) or an early adrenal tumor could not be excluded. Urinalysis including culture showed glucosuria and isosthenuria but no bacterial cystitis. As

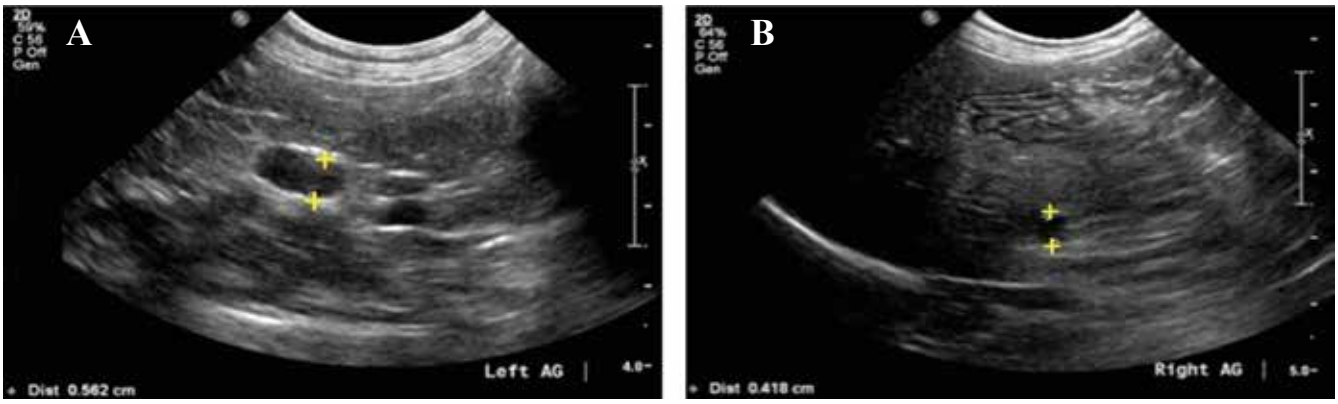

Figure 3. Ultrasound image of the adrenal glands. A. Longitudinal image of the left adrenal gland, and B. transverse image at the level of the caudal pole of the right adrenal gland. The calipers (yellow ++) indicate the height of the caudal pole.

the dose of insulin administered was not yet at a level suggestive of insulin resistance (>1.5 IU/kg BID), the initial advice was to increase the dose of glargine to 4.5 IU BID (0.8 IU/kg), to treat the stomatitis (detartration and extraction of affected teeth) and to promote weight loss (Sparkes et al., 2015). Insulin management errors were considered and ruled out. Other causes of insulin resistance and additional work-up were discussed with the owner in case no improvement would be observed.

Four weeks later (day 27), the cat was receiving 5 IU BID (0.95 IU/kg) of glargine but the same signs were still present. A low dose (0.1 mg/kg) dexamethasone suppression test (LDDST) was performed and confirmed HC (Table 2). In some cases, this test can also allow to make a differentiation between pituitary-dependent (PDH) and adrenal-dependent HC (ADH) based on the level of suppression of cortisol. In this case, there was suppression after four hours (<40 nmol/L) and an escape of suppression after eight

Table 1. The main differences of hypercortisolism between dogs and cats (Bhatti and Daminet, 2004; Nelson, 2014; Boland and Barrs, 2017).

	Dogs		Cats
Signalment	Breed predisposition	≠	No breed predisposition
	Older dogs	=	Older cats (>10 years)
	More in female dogs	≠	More male cats (54%)
Location	PDH (85%)	=	PDH (85%)
	ADH (15%)		ADH (15%)
History	Some have DM (10%)	≠	Most have DM (80%)
Clinical signs and physical examination (common findings)	Pupd	=	Pupd
	Polyphagia		Polyphagia
	Abdominal distention		Abdominal distention
	Endocrine alopecia		Endocrine alopecia
	Weakness		Lethargy
	Hepatomegaly		Hepatomegaly
	Epidermal atrophy		1/3 have extreme skin fragility
	Panting	≠	Weight loss
ALF	Often iso-enzym is induced	≠	No increase of iso-enzym
USG	Markedly decreased	≠	Usually > 1.020
Endocrine tests	LDDST (0,01 mg/kg IV)	≠	LDDST (0,1 mg/kg IV)
	UCCR	=	UCCR
Medical therapy	Trilostane	=	Trilostane

Table 2. Results of low dose dexamethasone suppression test (LDDST) in a fourteen-year-old cat with diabetes and suspicion of hypercortisolism. A value > 40 nmol/L, 8 hours after dexamethasone administration, is consistent with HC (Boland and Barrs, 2017).

Sample 1 (T0)	Sample 2 (4h)	Sample 3 (8h)
69 nmol/l	39 nmol/l	55 nmol/l

Table 3. Results of ACTH stimulation tests, used as follow-up in a fourteen-year-old cat with hypercortisolism treated with trilostane. Day 0 = first presentation in clinic.

Day of test	Dose trilostane	Dose trilostane after test	Sample 1: basal cortisol	Sample 2: post-ACTH
54	10 mg BID	10 mg BID	22 nmol/l	105 nmol/l
138	10 mg BID	8 mg BID	11 nmol/l	41 nmol/l
257	8 mg BID	7 mg BID	17 nmol/l	30 nmol/l
383	7 mg BID	5 mg BID	8 nmol/l	19 nmol/l
453	5 mg BID	5 mg BID	25 nmol/l	52 nmol/l
474	5 mg BID	0 mg	30 nmol/l	50 nmol/l

hours of administering dexamethasone. This is suggestive of PDH (Feldman, 2014; Boland and Barrs, 2017). This finding was compatible with the clinical signs and the poorly controlled DM. Diagnostic imaging was advised but declined by the owners. Both surgical and medical options were discussed. The owners elected a medical treatment with trilostane (Vetoryl®, Dechra Limited, North Yorkshire, UK; 10 mg BID). The dose of glargine was lowered to 4 IU BID because the treatment of HC could lead to an improved sensitivity to insulin.

A control examination four weeks later (day 54) revealed some improvement of the pupd. The results of HMBG showed constant hyperglycemia with a nadir of 18.6 mmol/L. Serum biochemistry revealed mild azotemia (creatinine 153 µmol/L, IRIS stage II). This has been previously described in cats on trilostane therapy (Mellett Keith et al., 2013). Thoracic radiographs were performed for further work-up of poorly controlled diabetes mellitus and for detection of potential concurrent abnormalities. No clinically significant abnormalities were found. An ACTH-stimulation test showed an optimal post-ACTH cortisol level (Table 3). It is recommended to perform this test four to six hours after administration of trilostane (Neiger et al., 2004). The aim of treatment should be clinical improvement in combination with post-ACTH serum cortisol concentrations between 50 and 150 nmol/L (Niessen et al., 2013). Electrolytes in the present case were within normal limits. The same dose of trilostane was continued. The dosage of glargine was increased to 5 IU BID.

At the next control examination, six weeks later (day 103), pupd was still present. HMBG still showed an insufficient glycemic control, hence the dose of glargine was increased (6 IU BID). Mild azotemia persisted. Urinalysis was advised but was difficult to perform because of the cat's aggressive nature.

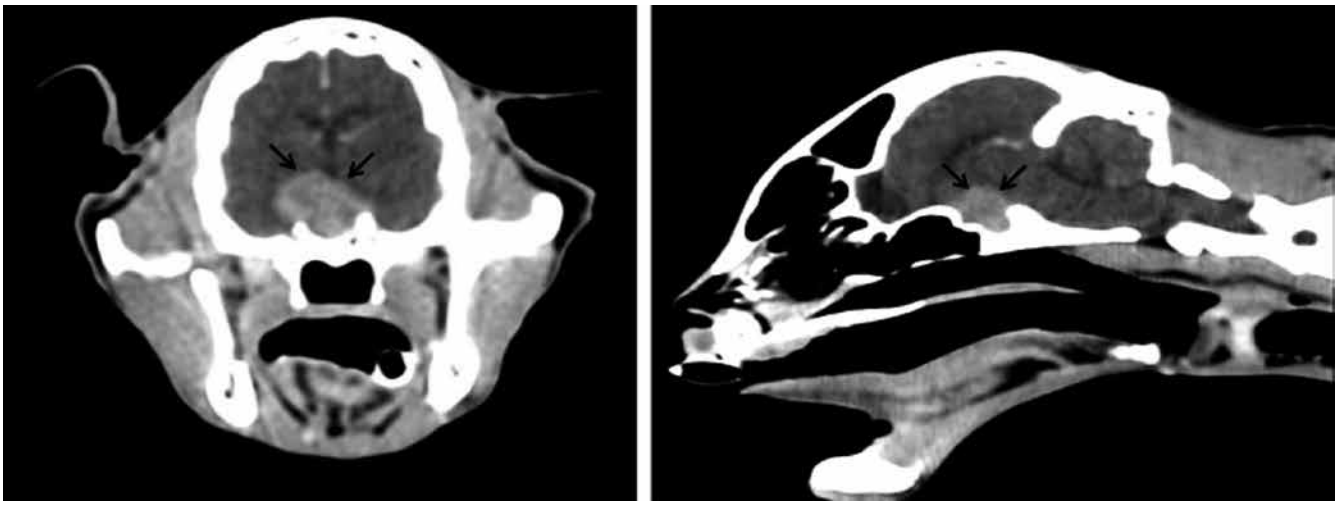

Figure 4. Post-contrast computed tomographic images (transverse image on the left side and mid sagittal image on the right side) showing a strongly, mildly heterogeneously, enhancing mass lesion in the pituitary fossa corresponding to a pituitary macroadenoma (black arrows).

Table 4. Sensitivity and specificity of tests that can be performed on cats to detect and/or differentiate hypercortisolism.

Test	Reference	N	Sensitivity	Specificity	Remarks
LDDST	Niessen et al. (2013)	/	Very good	Poor	
	Chiaramonte and Greco (2007)	/	/	/	Test of choice by many authors
	Feldman (2014)	58	100 %	Was not critically assessed	47 cats of their series and 11 cats from the literature: Immink et al. (1992) (two cats) – Goossens et al. (1995) (three cats) – Meij et al. (2001) (three cats) – Neiger et al. (2004) (three cats)
	Valentin et al. (2014)	28	/	/	Twenty-seven of twenty-eight tests were consistent with HAC and one was equivocal
ACTH stimulation test	Niessen et al. (2013)	/	Lack	/	In two thirds, the cortisol is in normal range
	Chiaramonte and Greco (2007)	/	/	/	Only 50-60 % with HAC show exaggerated response to ACTH administration
	Feldman (2014)	65	33 %	Questionable	51 cats of their series and 14 cats from the literature: Immink et al. (1992) (one cat) – Schwedes (1997) (one cat) – Watson and Herrtage (1998) (five cats) – Moore et al. (2000) (one cat) – Skelly et al. (2003) (one cat) – Neiger et al. (2004) (five cats)
	Valentin et al. (2014)	37	All samples : 56 % At 60 min 89 %	At 30 min : 89 % At 60 min: 89 %	
UC/CR	Niessen et al. (2013)	/	Most sensitive screening test	/	Elevated UC/CR could be result of concurrent illness and stress
	Chiaramonte and Greco (2007)	/	/	/	Also high in cats with non-adrenal illness and so, is false-positive high. High cortisol:creatinine ratio in cats with concurrent disease should be confirmed with a LDDST (0,1 mg/kg
	Feldman (2014)	48	Ok	Not ok	They included 28 cats of their series and 20 cats from the literature: Goossens et al. (1995) (six cats) - Schwedes (1997) (one cat) - Skelly et al. (2003) (one cat) - Meij et al. (2001) (seven cats) - Neiger et al. (2004) (five cats)
	Goossens et al. (1995)	6	Sensitive	Not mentioned	

On day 138, the ACTH-stimulation test revealed a low post-ACTH cortisol level (Table 3). The dose of trilostane was decreased to 8 mg BID (pharmaceutically compounded). The HMBG curve showed periods of hypoglycemia and the dose of insulin was decreased to 4 IU BID. The azotemia (202.4 µmol/L, IRIS stage II) was mildly increased compared to the previous control, and ideally, a urinalysis should have been performed, but was again impossible because of the cat's aggressive nature. It was advised to make a mix of diabetic and renal food (50/50) because of the high protein levels in the diabetic food.

The next control examination on day 257 (Table 3) again led to a decrease of the trilostane (7 mg BID) and glargine (1.5 IU BID) dose. Urinalysis showed renal proteinuria (UPC 0.52, inactive sediment, negative culture) and isosthenuria (1,014). The mild azotemia was still present. However, according to the owners, pupd was significantly decreased.

During the next three months, the insulin therapy was tapered and could finally be stopped. More than one year after the first consultation, remission of dia-

betes mellitus was suspected. Weekly monitoring of the glucose level, four hours after each meal, was recommended to detect possible relapse of diabetes mellitus. A month after stopping the insulin therapy (day 383), a control ACTH-stimulation test showed again a low post-ACTH cortisol level (< 50 nmol/L) and the dose of trilostane was decreased to 5 mg BID (Table 3). The azotemia (creatinine 222 µmol/L, IRIS stage II) was stable to mildly progressive and a control urinalysis showed borderline proteinuria. The owners mentioned pupd and weight loss. Because the cat was in diabetic remission and the azotemia was mildly progressive, the diet was changed to a strictly renal diet. Stopping diabetic diet can increase the risk of relapse; however, a renal diet was elected because the progressive azotemia was estimated to be more important (Sparkes et al., 2015). Thyroxine (T4) concentration, to exclude concomitant hyperthyroidism because of the weight loss, was within the reference range.

On day 453, the cat presented with compulsive behavior; walking around the table aimlessly. A plantigrade stance was present. Eating and drinking behavior was normal, but weight loss was noticed (400 g). The cat received trilostane 5 mg BID and the ACTH-stimulation test showed a good control of HC (Table 3). The owners declined further diagnostic imaging.

During the next month, the neurological signs worsened and the cat developed an unsteady gait. On day 474, the post-ACTH cortisol level was borderline and trilostane was stopped because of deterioration of the general condition of the cat (Table 3). The neurological signs disappeared but one month later, the cat started to circle to the right. He also seemed blind. The temporarily improvement of the clinical signs was probably because stopping trilostane caused an increase in serum cortisol and hence the symptoms were reduced. Since the history of HC and the current neurological signs, there was a suspicion of a macroadenoma and a CT-scan was re-advised. The CT scan (day 562) confirmed a large asymmetric, strongly contrast-enhancing mass in the pituitary fossa extending dorsally out of the sella turcica (Figure 4). Treatment options were discussed with the owner. Considering the life-quality and life expectancy, the owners elected euthanasia.

DISCUSSION

Insulin resistance is defined as present in a cat with poorly controlled DM on an insulin dosage greater than 1.5 IU/kg per injection (Scott-Moncrieff, 2010; Caney, 2013). It is important to differentiate insulin resistance from other causes of poor glycemic control, such as administration difficulties and insulin-related factors. A thorough history and demonstration of an injection by the owner may help to exclude many interfering factors. If no management problem can be found, further investigations are required (Scott-Moncrieff, 2010; Sparkes et al., 2015).

Assessment for concurrent diseases includes urinalysis and culture, hematology and serum biochemistry, abdominal imaging and thoracic radiographs. Serum feline pancreatic lipase measurement can be valuable in the diagnosis of pancreatitis. Especially hypersomatotropism (acromegaly) but also HC are important causes of severe insulin resistance. Hypersomatotropism is evaluated by a measurement of serum insulin-like growth factor-1. In this case, hypersomatotropism was considered highly unlikely due to IGF-1 measurement, performed several months after the insulin treatment had been started (Caney, 2013; Roomp and Rand, 2013; Sparkes et al., 2015; Ramsey and Herrtage, 2017). Since the hepatic growth hormone receptors are stimulated by insulin for the production of IGF-1, the concentrations of IGF-1 may be low in untreated diabetic cats and may increase during treatment with insulin. Therefore, it is important to treat diabetic cats first, before measurement of IGF-1 (Reusch et al., 2006; Ramsey and Herrtage, 2017).

There are multiple tests to diagnose HC in cats. All have advantages and disadvantages. In Table 4, their sensitivity and specificity are listed up. The LDDST is based on suppression of the cortisol level by administration of dexamethasone in normal cats. Cats need a higher dose of dexamethasone (0.1 mg/kg intravenously) than dogs because a high percentage of normal cats do not experience the suppressive effects of dexamethasone in lower dose (Chiaramonte and Greco, 2007; Scott-Moncrieff, 2010; Niessen et al., 2013). An ACTH stimulation test can also be used for screening. This test is based on the adrenal glands producing excessive amounts of cortisol after stimulation in cats with HC compared to normal cats (Niessen et al., 2013). Urine cortisol/creatinine ratio (UCCR) can be used as an initial screening test. Additionally, the ratio can be used to differentiate between pituitary-dependent (PDH) and adrenal-dependent HC (ADH), if the suppression test with dexamethasone is performed. The advantage of this test is that it can be performed at home by collecting morning urine. If there is more than 50 % of suppression of the average UCCR after administration of dexamethasone, it is suggestive for PDH (Goossens et al., 1995; Niessen et al., 2013). The reference range for UCCR and cortisol post-ACTH is laboratory specific. There are other tests like measuring endogenous adrenocorticotropic hormone (ACTH) and pro-opiomelanocortin, but these will not be further discussed (Niessen et al., 2013). In this case, a LDDST was suggestive of PDH.

Besides endocrine testing, medical imaging is advised. Abdominal ultrasonography, CT and MRI can be used to image the adrenal glands and the pituitary gland. Reports on ultrasound of the adrenal glands of cats with PDH are limited. Similar to dogs, the majority of cats with PDH show bilateral enlargement of the adrenal glands with retention of the normal shape. However, few cases with normal sized adrenal glands or mild asymmetric enlargement, as described in this

case report, have been reported. (Combes et al., 2013; Valentin et al. 2014; Boland and Barrs, 2017). In cats with ADH, the most important finding is a unilateral adrenal mass, with normal or small contralateral gland (Valentin et al., 2014; d'Anjou and Penninck, 2015; Boland and Barrs, 2017). The pituitary gland can be visualized by CT and MRI. About 50 % of pituitary tumors are large enough in size to visualize (Chiaramonte and Greco, 2007; Niessen et al., 2013; Boland and Barrs, 2017). Generally, tumors smaller than 10 mm in height are considered microtumors, whereas the larger masses are macrotumors. Microtumors are challenging to diagnose on imaging, whereas macrotumors are well-defined, strongly contrast-enhancing masses in the sellar region (Wisner and Zwingerberger, 2015).

The cat described in this case report was treated with lente insulin after initial diagnosis of DM and then switched to a longer-acting insulin (glargine). At the time the cat was examined, only one insulin with a veterinary license for cats was available in Belgium, i.e. Caninsulin® (MSD Animal Health, Brussels, Belgium). It is a porcine insulin zinc suspension with an insulin concentration of 40 IU/ml. Because of the poor control of DM, and because glargine and protamine zinc insulin (PZI) have a longer duration of action, the treatment was changed to glargine by the referring veterinarian. At time of diagnosis and follow-up, PZI was not registered in Belgium. Glargine is a long-acting synthetic insulin analogue. PZI has a similar duration of action as glargine in healthy cats (Marshall et al., 2008). A difference between PZI and glargine is the time to reach the first nadir glucose concentration. This is significantly shorter for PZI than for glargine but the time to reach the last nadir is similar, i.e. 14 hours (Marshall et al., 2008). Currently, proZinc® (Boehringer Ingelheim, Ingelheim, Germany) is available in Belgium. In several studies, a better glycemic control and higher remission rates with glargine and PZI have been suggested than with lente insulin (Boari et al., 2008; Marshall et al., 2009; Nelson et al., 2009; Roomp and Rand, 2009). However, it should be emphasized that the current level of evidence of all studies is moderate to poor. Common reasons of bias are lack of randomization and blinding, poor study design and small sample size (Gostelow et al., 2014).

In the literature, a dose of insulin > 1.5 IU/kg per injection is considered a cut-off value for insulin resistance, although it is often recommended to investigate causes of poorly controlled DM at lower dosages of insulin, like in this case (Sparkes et al., 2015). In the present case, HC was diagnosed and medical treatment was started with trilostane. Trilostane is an inhibitor of the 3β-hydroxysteroid dehydrogenase enzyme. This enzyme has an essential role in the synthesis of steroids (Ramsey and Herrtage, 2017). There are currently no pharmacokinetic data available for trilostane in cats and only few reports of cats with HC treated with trilostane. In two case reports, each on one cat (i. e. one cat with PDH and one cat with bilateral adrenal enlargement with excessive sex hormone production), improvement of clinical signs has been described. In both cases, the initial dosage was 30 mg once daily (Skelly et al., 2003; Boag et al., 2004). In the cat with PDH, the dosage was increased to 30 mg twice daily. Therapy was stopped when the cat became anorexic. An ACTH stimulation test was not performed, so iatrogenic hypocortisolism could not be ruled out. The cat died of renal failure. It was not clear if renal toxicity due to trilostane was involved (Skelly et al., 2003). A study on five cats with PDH described two cats that died after 16 and 140 days but three others were still alive after 6, 11 and 20 months, respectively. Three cats were diagnosed with DM but continued to require insulin after treatment with trilostane was started. In all cats, a few days after starting trilostane therapy, clinical signs were improved. Final dosages of 5.4 mg/kg once daily and 7 mg/kg twice daily were used (Neiger et al., 2004). The largest and most recent study by Mellett Keith et al. (2013) included fifteen cats with spontaneous HC; fourteen cats were diagnosed with PDH and one cat with ADH. An improvement of the clinical signs and of the ACTH stimulation test results was described in 13 of the 15 cats. In that study, diabetes mellitus was reported in 9/15 cases. In 6/9 cats with diabetes the insulin requirements could be decreased by 36 % within two months. The median survival time was 617 days for all cats. The mean final dose of trilostane used, was 2.7 mg/kg once daily and 5.6 mg/kg twice daily. Four cats had changes consistent with chronic kidney disease (CKD) on medical imaging (Mellett Keith et al., 2013). Compared to the previous case reports, the cat in the current case was treated with a lower dose of trilostane (+/- 2 mg/kg twice daily starting dose), which could be tapered based on clinical improvement and ACTH stimulation test results. Possible explanations for this difference could be an increased awareness of the disease in cats, and therefore diagnosis at an earlier stage, lower starting dosage of trilostane, as well as improved follow-up by routine performance of ACTH stimulation tests. A similar evolution has been observed in dogs treated for hyperadrenocorticism, as the initial manufacture's starting dose recommendation (3-6 mg/kg once daily) was much higher than the currently advised dose (2 mg/kg once daily) of Vetoryl® (Dechra Limited, North Yorkshire, UK) (Pérez-Alenza and Melian, 2017). In the current case, the cat developed progressive azotemia during treatment. It should be emphasized that before treatment, the urine specific gravity (USG) was 1.015 although the majority of cats with HC have a USG of >1.020 (Feldman, 2014; Boland and Barrs, 2017). It is unclear if the azotemia was caused by therapy or if the CKD had already been developing before treatment.

Up till now, no cases have been reported where remission of DM occurs in cats with HC treated with

trilostane. However, the cat in this case went into remission after 356 days of therapy with trilostane. At day 474, trilostane was stopped because of deterioration of the general condition of the cat. Iatrogenic hypoadrenocorticism, due to necrosis of the adrenal gland cortex, appeared less likely based on ACTH-stimulation test results (Ramsey, 2010).

No studies have been published in cats on the optimal timing to perform an ACTH stimulation test after drug administration. Based on studies in dogs and a similar cortisol nadir after trilostane administration in dogs and cats, a similar timing for the ACTH stimulation test seems justified in cats (four to six hours after trilostane administration) (Neiger et al. 2004). Post-ACTH serum cortisol concentrations should be between 50 and 150 nmol/L. These values are laboratory specific (Niessen et al., 2013). Trilostane is the medical treatment recommended above all other medical options because of its superior efficacy, relative lack of side effects and ease of use. Other medical treatment options are mitotane, ketoconazole, aminoglutethimide and metyrapone but they are not recommended due to the lack of efficacy in some cats, their adverse effects and the difficulty of sourcing them (Niessen et al., 2013; Boland and Barrs, 2017).

Surgical treatment of feline HC depends on the type of HC. If a single adrenal tumor is present, adrenalectomy is recommended. Bilateral removal of the adrenal glands has been described in case of bilateral adrenal tumors or PDH; however, in that case, the patient needs to be treated for hypoadrenocorticism after the removal (Chiaramonte and Greco, 2007; Niessen et al., 2013). Hypophysectomy is the best theoretical option in cats with PDH (Meij et al., 2001; Bhatti and Daminet, 2004; Niessen et al., 2013). In one study, microsurgical transsphenoidal hypophysectomy has been described in seven cats with HC (Meij et al., 2001). Two cats died within four weeks after surgery. The other five cats went into both clinical and biochemical remission of HC two months after hypophysectomy with a median survival time of 15 months with a range of 6 to 46 months; two of the cats were still alive at the time of publication. One cat showed recurring signs of HC 19 months after surgery. The most important postoperative complications were oronasal fistula, transient reduction of tear production and wound dehiscence of the soft palate. Meij et al. (2001) concluded that a learning curve is necessary when treatment of PDH with hypophysectomy is introduced but that it may offer a better quality of life and a higher survival rate than bilateral adrenalectomy or medical management. The owner initially refused advanced medical imaging and surgical treatment. The overall survival time in this case was 535 days since the diagnosis of HC. Based on the described case and previous publications, medical treatment could be a valuable alternative to surgical treatment in cats with HC (Skelly et al., 2003; Boag et al., 2004; Neiger et al., 2004; Mellet Keith et al., 2013).

Although time-consuming and expensive, radiation therapy is another treatment option (Chiaramonte and Greco, 2007). Only a small number of cats treated with pituitary irradiation have been described in the veterinary literature; however, the results indicate it could be a valuable option (Mayer et al., 2006). The median survival time in a study with eight cats was 523 days, another study with five cats had survival rates of 5.5, 8, 15, 18, 20.5 months. Alopecia, color change of hair, hair depigmentation, atrophy of the epidermis and epilation in the treatment field are described complications (Kaser-Hotz et al., 2002; Mayer et al., 2006). In the study by Mayer et al. (2006), in one cat out of eight, an acute aural adverse effect was seen. Bilateral cataracts, most likely an adverse effect of radiation therapy, was diagnosed in one cat of eight, thirteen months after treatment (Mayer et al., 2006). Similarly, as the median survival time with trilostane treatment is approximately 600 days and seems to be overall well-tolerated (cf. the current case and previous publications), medical treatment of HC in cats could be a valuable alternative (Neiger et al., 2004; Mellett Keith et al., 2013).

In the study of Mayer et al. (2006), in only four of the eight cats, follow-up brain imaging was performed: two cats had a decreased tumor size at six and eight months after radiation and two cats had unchanged tumor size at three and five months, respectively. Kaser-Hotz et al. (2002) described follow-up CT examination performed in four cats. In one cat, the mass had disappeared, and in three cats, the mass was stable or had decreased slightly in size. The ideal treatment protocol with radiation still needs to be established (Kaser-Hotz, 2002; Mayer et al., 2006; Chiaramonte and Greco, 2007).

CONCLUSION

In the present case report, a cat with combined diabetes mellitus and HC medically treated with long-acting insulin and trilostane is described. HC is rare in cats but important to consider in case of insulin resistance. The cat in this report was successfully treated with trilostane and had a good quality of life. Diabetic remission was achieved.

REFERENCES

Bhatti S., Daminet, S. (2004). Mogelijkheden voor de behandeling van hypercortisolisme bij hond en kat. *Vlaams Diergeneeskundig Tijdschrift 73*, 344-350.

Boag A.K., Neiger R., Church D.B. (2004). Trilostane treatment of bilateral adrenal enlargement and excessive sex steroid hormone production in a cat. *Journal of Small Animal Practice 45,* 263-266.

Boari A., Aste G., Rocconi F., Dalessandri A., Vita S. (2008). Glargine insulin and high-protein-low-carbohydrate diet in cats with diabetes mellitus. *Veterinary Research Communications 32*, 243-245.

Boland L.A., Barrs V.R. (2017). Peculiarities of Feline Hyperadrenocorticism. Update on diagnosis and treatment. *Journal of Feline Medicine and Surgery 19*, 933-947.

Caney S.M.A. (2013). Management of cats on lente insulin: tips and traps. *Veterinary Clinics of North America: Small Animal Practice 43*, 267-282.

Chiaramonte D., Greco D.S. (2007). Feline Adrenal Disorders. *Clinical Techniques in Small Animal Practice 22*, 26-31.

Combes A., Pey P., Paepe D., Rosenberg D., Daminet S., Putcuyps I., Bedu A., Duchateau L., de Fornel-Thibaud P., Benchekroun G., Saunders J.H. (2012). Ultrasonographic appearance of adrenal glands in healthy and sick cats. *Journal of Feline Medicine and Surgery 15*, 445-457.

d'Anjou M., Penninck D. (2015). Adrenal glands. In: Penninck D., d'Anjou M. (editors). *Atlas of Small Animal Ultrasonography*. Second edition, Wiley Blackwell, p. 387-401.

Feldman E.C. (2014). Hyperadrenocorticism in cats. In: Feldman E.C., Nelson R.W., Reusch C., Scott-Moncrieff J.C. (editors). *Canine and Feline Endocrinology*. Fourth edition, Elsevier Saunders, Missouri, p. 452-478.

Goossens M.M.C., Meyer H.P., Voorhout G., Sprang E.P.M. (1995). Urinary excretion of glucocorticoids in the diagnosis of hyperadrenocorticism in cats. *Domestic Animal Endocrinology 12*, 355-362.

Gostelow R., Forcada Y., Graves T., Church D., Niessen S. (2014). Systematic review of feline diabetic remission: Separating fact from opinion. *The Veterinary Journal 202*, 208-221.

Kaser-Hotz B., Rohrer C.R., Stankeova S., Wergin M., Fidel J., Reusch C. (2002). Radiotherapy of pituitary tumours in five cats. *Journal of Small Animal Practice 43*, 303-307.

Marshall R.D., Rand J.S., Morton J.M. (2008). Glargine and protamine zinc insulin have a longer duration of action and result in lower mean daily glucose concentrations than lente insulin in healthy cats. *Journal of Veterinary Pharmacology and Therapeutics 31*, 205-212.

Marshall R.D., Rand J.S., Morton J.M. (2009). Treatment of newly diagnosed diabetic cats with glargine insulin improves glycaemic control and results in higher probability of remission than protamine zinc and lente insulins. *Journal of Feline Medicine & Surgery 11*, 683-691.

Mayer M.N., Greco D.S., LaRue S.M. (2006). Outcomes of pituitary tumor irradiation in cats. *Journal of Veterinary Internal Medicine 20*, 1151-1154.

Meij B.P., Voorhout G., Ingh T.S., Rijnberk A.D. (2001). Transsphenoidal hypophysectomy for treatment of pituitary-dependent hyperadrenocorticism in 7 cats. *Veterinary Surgery 30*, 72-86.

Mellett Keith A.M., Bruyette D., Stanley, S. (2013). Trilostane therapy for treatment of spontaneous hyperadrenocorticism in cats: 15 cases (2013). *Journal of Veterinary Internal Medicine 27*, 1471-1477.

Neiger R., Witt A.L., Noble A., German A.J. (2004). Trilostane therapy for treatment of pituitary-dependent hyperadrenocorticism in 5 cats. *Journal of Veterinary Internal Medicine 18*, 160-164.

Nelson R.W., Henley K., Cole C. (2009). Field safety and efficacy of protamine zinc recombinant human insulin for treatment of diabetes mellitus in cats. *Journal of Veterinary Internal Medicine 23*, 787-793.

Nelson R.W. (2014). Endocrine disorders. In: Nelson R.W. and Couto C.G. (editors). *Small Animal Internal Medicine*. Fifth edition, Elsevier Health Sciences, Missouri, p. 798-854.

Niessen S.J., Church D.B., Forcada Y. (2013). Hypersomatotropism, acromegaly, and hyperadrenocorticism and feline diabetes mellitus. *Veterinary Clinics of North America: Small Animal Practice 43*, 319-350.

Pérez-Alenza D., Melian C. (2017). Hyperadrenocorticism in dogs. In: Ettinger S.J., Feldman E.C. and Côté E. (editors). *Textbook of Veterinary Internal Medicine*. Eighth edition, Saunders Elsevier, Missouri, p. 1795-1811.

Ramsey I.K. (2010). Trilostane in dogs. *Veterinary Clinics of North America: Small Animal Practice 40*, 269-283.

Ramsey I.K., Herrtage M. (2017). Feline hyperadrenocorticism. In: Ettinger S.J., Feldman E.C. and Côté E. (editors). *Textbook of Veterinary Internal Medicine*. Eighth edition, Saunders Elsevier, Missouri, p.1811-1818.

Rand J.S. (2013). Pathogenesis of feline diabetes. *Veterinary Clinics of North America: Small Animal Practice 43*, 221-231.

Rand J., Gottlieb S.A. (2017). Feline diabetes mellitus. In: Ettinger S.J., Feldman E.C. and Côté E. (editors). *Textbook of Veterinary Internal Medicine*. Eighth edition, Saunders Elsevier, Missouri, p. 1781-1795.

Reusch C.E., Kley S., Casella M., Nelson R.W., Mol J., Zapf J. (2006). Measurements of growth hormone and insulin-like growth factor 1 in cats with diabetes mellitus. *Veterinary Record 158*, 195-200.

Roomp K., Rand J. (2009). Intensive blood glucose control is safe and effective in diabetic cats using home monitoring and treatment with glargine. *Journal of Feline Medicine & Surgery 11*, 668-682.

Roomp K., Rand J.S. (2013). Management of diabetic cats with long-acting insulin. *Veterinary Clinics of North America: Small Animal Practice 43*, 251-266.

Scott-Moncrieff J.C. (2010). Insulin resistance in cats. *Veterinary Clinics of North America: Small Animal Practice 40*, 241-257.

Skelly B.J., Petrus D., Nicholls P.K. (2003). Use of trilostane for the treatment of pituitary-dependent hyperadrenocorticism in a cat. *Journal of Small Animal Practice 44*, 269-272.

Sparkes A.H., Cannon M., Church D., Fleeman L., Harvey A., Hoenig M., Peterson M.E., Reusch C.E., Taylor S., Rosenberg D. (2015). ISFM consensus guidelines on the practical management of diabetes mellitus in cats. *Journal of Feline Medicine and Surgery 17*, 235-250.

Vetoryl, Dechra Limited, North Yorkshire, United Kingdom (2015).

Valentin S.Y., Cortright C.C., Nelson R.W., Pressler B.M., Rosenberg D., Moore G.E., Scott-Moncrieff J.C. (2014). Clinical findings, diagnostic test results, and treatment outcome in cats with spontaneous hyperadrenocorticism: 30 cases. *Journal of Veterinary Internal Medicine 28*, 481-487.

Wisner E., Zwingenberger A. (2015). Sellar and parasellar region. In: Wisner E., Zwingenberger A. (editors). *Atlas of Small Animal CT and MRI*. First edition, Wiley Blackwell, p. 244-263.