The Veterinary Journal 270 (2021) 105623

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Pituitary tumour types in dogs and cats

K. Sanders*, S. Galac, B.P. Meij

Department of Clinical Sciences, Faculty of Veterinary Medicine, Utrecht University, Yalelaan 108, 3584 CM Utrecht, The Netherlands

ARTICLE INFO

Article history:
Accepted 19 January 2021

Keywords:
Cushing's disease
Hypercortisolism
Hypersomatotropism
Pituitary adenoma
Veterinary

ABSTRACT

Pituitary tumours are common in dogs and are being increasingly recognized in cats. Pituitary tumours are usually classified as adenomas and should only be classified as carcinomas when there is evidence of metastatic spread of the tumour, which is rare. Despite the benign nature of most pituitary tumours, they can still compress or invade neighbouring tissues. Pituitary tumours can be functional (hormonally active) or non-functional (hormonally silent). The aim of this review was to provide an overview of the different pituitary tumour types in dogs and cats that have been reported in the literature. In dogs, the most common pituitary tumour type is the corticotroph adenoma, which can cause pituitary-dependent hypercortisolism. In cats, the most common pituitary tumour is the somatotroph adenoma, which can cause hypersomatotropism, and the second-most common is the corticotroph adenoma. A lactotroph adenoma has been described in one dog, while gonadotroph, thyrotroph and null cell adenomas have not been described in dogs or cats. Hormonally silent adenomas are likely underdiagnosed because they do not result in an endocrine syndrome. Tools used to classify pituitary tumours in humans, particularly immunohistochemistry for lineage-specific transcription factors, are likely to be useful to classify canine and feline pituitary tumours of unknown origin. Future studies are required to better understand the full range of pituitary adenoma pathology in dogs and cats and to determine whether certain adenoma subtypes behave more aggressively than others. Currently, the mechanisms that underlie pituitary tumorigenesis in dogs and cats are still largely unknown. A better understanding of the molecular background of these tumours could help to identify improved pituitary-targeted therapeutics.

Introduction

Of all intracranial tumours, pituitary tumours account for approximately 13% in dogs (Snyder et al., 2006, 2008) and 9% in cats (Troxel et al., 2003), compared to 10–17% in humans (Jagannathan et al., 2007; Ostrom et al., 2018). Pituitary tumours most frequently arise from the adenohypophysis (Troxel et al., 2003; Meij et al., 2010a; Polledo et al., 2018). Other masses in the sellar region may include craniopharyngioma, Rathke's cleft cyst, metastasis or ingrowth of a different tumour, secondary neoplasm, hypophysitis, or pituicytoma (Kleinschmidt-DeMasters, 2016; Miller et al., 2018a).

The presence and distribution of different pituitary tumour types in humans have been well-described and reviewed, but this is not the case for dogs and cats. The aim of this review was to provide an overview of the different pituitary tumour types in dogs and cats that have been reported in the literature. We will first review the form and function of the normal pituitary gland, and pituitary tumour type classification in humans. Thereafter, we will discuss some clinical aspects and, when applicable, the potential pathogenesis of canine and feline tumours.

The form and function of the normal pituitary

The pituitary gland (*hypophysis cerebri*) is the core element of the endocrine system. It controls fundamental processes such as metabolism, reproduction, growth and stress response (Davis et al., 2013). The pituitary gland is composed of three functional units: the anterior lobe (AL; *pars distalis* and *pars tuberalis*), the intermediate lobe (IL; *pars intermedia*) and the posterior lobe (PL; *pars nervosa*). The AL and IL together form the adenohypophysis, while the PL forms the neurohypophysis (Meij et al., 2010a). During embryonic development, a structure called Rathke's pouch arises from the roof of the developing mouth, which subsequently separates from the oral cavity and further develops into the AL and IL of the adenohypophysis (Rizzoti and Lovell-Badge, 2005). The *pars distalis* of the AL is separated from the IL by a lumen called Rathke's cleft, which is the remnant of the lumen of Rathke's pouch (Meij et al., 2010a).

* Corresponding author.
E-mail address: k.sanders@uu.nl (K. Sanders).

http://dx.doi.org/10.1016/j.tvjl.2021.105623

The *pars distalis* of the AL contains five different hormone-secreting cell types: corticotroph cells that secrete adrenocorticotropic hormone (ACTH); gonadotroph cells that secrete luteinizing hormone (LH) and/or follicle-stimulating hormone (FSH); thyrotroph cells that secrete thyroid-stimulating hormone (TSH), lactotroph cells that secrete prolactin (PRL); and somatotroph cells that secrete growth hormone (GH) (Fig. 1) (Meij et al., 2010a; Cox et al., 2017). The IL contains melanotroph cells that secrete α-melanocyte-stimulating hormone (α-MSH) (Cox et al., 2017). Both corticotroph and melanotroph cells synthesize the precursor molecule proopiomelanocortin (POMC) (Bicknell, 2008). In the corticotroph cells of the AL, POMC is cleaved into multiple peptides including ACTH by an enzyme called prohormone convertase 1 (PC1/3). In the melanotroph cells of the IL, ACTH is further cleaved into α-MSH and corticotropin-like intermediate peptide (CLIP) by prohormone convertase 2 (P2) (Bicknell, 2008).

The differentiation of the hormone-secreting cells of the AL and IL is regulated by lineage-specific transcription factors. These transcription factors include T-box transcription factor TBX19 (TPIT) for the corticotroph and melanotroph cells; pituitary-specific positive transcription factor 1 (PIT1) for the thyrotroph, somatotroph and gonadotroph cells; and steroidogenic factor-1 (SF-1) for the gonadotroph cells (Fig. 1) (Al-Brahim and Asa, 2006; Faltermeier et al., 2019).

Pituitary tumour classification in humans

The World Health Organization (WHO) classifications provide international standards on the histological and molecular (sub) typing of human tumours. According to the 2017 *WHO Classification of Tumours of Endocrine Organs*, tumours of the adenohypophysis in humans are classified as either adenomas or carcinomas. Carcinomas cannot be defined by histopathological parameters, but only by demonstrating metastatic spread of the tumour. Metastases can be present both within and outside of the central nervous system, and are exceptionally rare (Al-Brahim and Asa, 2006; Mete and Lopes, 2017). Although pituitary tumours rarely metastasize, they can still cause significant problems by compressing or invading neighbouring neural and vascular tissues, and by excessive hormone secretion that can be fatal if not properly treated (Vankelecom and Roose, 2017).

Pituitary tumours can be either functional (hormonally active) or non-functional (hormonally silent). The 2017 WHO classification mostly focusses on immunohistochemical classification according to the hormone that the tumour expresses, and expression of aforementioned lineage-specific transcription factors. These transcription factors include TPIT, PIT1 and SF-1 (Fig. 1), which are preserved in pituitary tumours derived from these cells (Manojlovic-Gacic et al., 2019). The transcription factors enable more precise classification of tumours that do not express hormones or do so at a very low level. Tumours lacking both hormone expression and transcription factor expression are designated as null cell adenomas (Faltermeier et al., 2019).

In addition to immunohistochemical staining for hormones and transcription factors, others that can aid the diagnosis include reticulin staining to differentiate adenoma from healthy or hyperplastic adenohypophyseal tissue; Periodic-Acid-Schiff (PAS) staining to highlight ACTH-positive secretory granules; and low molecular weight cytokeratin (LMWC) immunohistochemistry (IHC) to distinguish densely granulated from sparsely granulated adenomas. The LMWC staining can also be used to detect Crooke's hyaline change which usually only occurs in non-tumorous corticotrophs and is a marker for systemic hypercortisolism. This hyaline change is rarely also seen in adenoma cells, in which case it

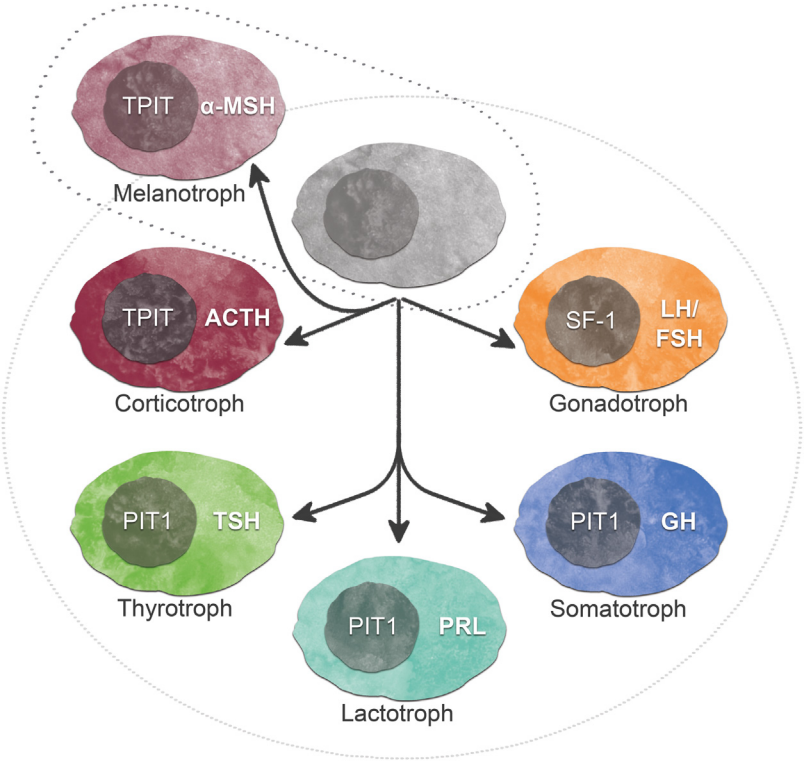

Fig. 1. Hormone-secreting cell types of the adenohypophysis. Cell types in the anterior lobe encircled with light grey dotted line, cell type in the intermediate lobe encircled with grey dotted line. The hormone that is secreted by the cell is indicated in bold in the cell cytoplasm, the corresponding lineage-specific transcription factors are indicated in the cell nucleus. TPIT, T-box transcription factor TBX19; ACTH, adrenocorticotropic hormone; SF-1, steroidogenic factor-1; LH, luteinizing hormone; FSH, follicle-stimulating hormone; PIT1, pituitary-specific positive transcription factor 1, TSH, thyroid-stimulating hormone, PRL, prolactin; GH, growth hormone.

is called a Crooke's cell adenoma (Al-Brahim and Asa, 2006; Mete and Lopes, 2017). The number of mitotic figures and the Ki-67 labelling index, both markers for proliferation, can be used to assess the proliferative and therefore possibly malignant potential (Mete and Lopes, 2017; Inoshita and Nishioka, 2018). Although examination of the tumour ultrastructure by electron microscopy (EM) was initially used to assess aspects such as granulation patterns, the use of aforementioned specific IHC staining can provide this information as well, which reduces the need for EM (Inoshita and Nishioka, 2018).

The most common subtype in humans is the lactotroph adenoma (30–50%), followed by the gonadotroph adenoma (15–40%, majority hormonally silent), the somatotroph adenoma (15–20%) and the corticotroph adenoma (15%) (Faltermeier et al., 2019). The need for the distinction between different subtypes in humans is further illustrated by the fact that several subtypes clinically show more aggressive behaviour than others. These subtypes are therefore indicated as "high-risk adenomas", and include the sparsely granulated somatotroph adenomas, Crooke's cell adenomas, hormonally silent corticotroph adenomas, lactotroph adenomas in males, and plurihormonal PIT1-positive adenomas (Mete and Lopes, 2017).

Pituitary tumour types in dogs and cats

Because pituitary tumours in dogs and cats also rarely metastasize, we suggest using the same classification as in humans, regardless of histopathological parameters: adenoma when no metastases can be detected, and carcinoma when metastases are present. Immunohistochemical staining for hormones are being increasingly performed, including staining for ACTH, α-MSH, GH, and PRL (Fletcher et al., 2016; Miller et al., 2018b; Polledo et al., 2018). Staining for lineage-specific transcription factors has not been reported in dogs or cats. This might be especially useful in tumours that stain negative for the aforementioned hormones. Whether there are certain subtypes that are clinically more aggressive than others in dogs and cats is currently unknown.

To provide an overview of the pituitary tumour types that have been reported in dogs and cats, we performed a literature search in the NCBI PubMed Central database in March and April 2020. The search terms that we used included pituitary/hypophysis; tumor/tumour/adenoma/carcinoma; dog/canine/canis familiaris; cat/feline/felis catus; corticotroph/ACTH, prolactinoma/lactotroph/prolactin, thyrotroph/TSH, gonadotroph/LH/FSH, somatotroph/GH. Cases were included when diagnostic imaging or necropsy indicated the presence of a pituitary mass, and/or when endocrine testing indicated the presence of a hypersecreting pituitary gland. Cases were excluded when pituitary origin of an endocrine syndrome was not confirmed, or when they were already included in a different article by the same research group. Tumours were classified as a specific subtype when endocrine testing and diagnostic imaging indicated a hypersecreting pituitary tumour, when the tumour subtype was analysed using IHC, or both. When a pituitary tumour was detected but no hormonal hypersecretion syndrome was reported or IHC did not stain positive for the tested hormone(s), the tumour was classified as unknown. The full list with the articles that were consulted to produce this overview is presented in Supplementary file (See Appendix A: Supplementary material). The summarizing overview is shown in Table 1.

It is emphasized that this overview is not a true representation of the actual subtype distribution in dogs and cats but indicates which subtypes have been characterized and described in literature. Setbacks of this approach include that we may underestimate the presence of several subtypes, including hormonally silent tumours because these will often remain undetected, and plurihormonal tumours because not all studies performed IHC and the tumours are often classified by the hormone that predominates the clinical syndrome. In addition, studies that screen for a specific endocrine syndrome can introduce potential bias. We have not made a distinction between corticotroph and melanotroph tumours because both can result in pituitary-dependent hypercortisolism (PDH), and IHC was not always performed to assess ACTH and/or α-MSH expression; nor have we made a distinction between adenomas and carcinomas, because different criteria were used in the published studies to make this distinction.

Table 1
Overview of pituitary tumour types in dogs and cats that have been reported in literature.

Species	Pituitary tumour type	Number of cases reported
Dog	Corticotroph	3387
	Somatotroph	4
	Lactotroph	1
	Plurihormonal	2
	Unknown	138
Cat	Somatotroph	393
	Corticotroph	126
	Double/plurihormonal	5
	Unknown	33

Corticotroph adenomas

Corticotroph adenomas are pituitary adenomas from the TPIT lineage that express ACTH. Corticotroph adenomas can excessively secrete ACTH, which results in PDH, also known as Cushing's disease (Sanders et al., 2018).

Dogs

In dogs, the vast majority of pituitary adenomas derive from the corticotroph lineage, which has been reported in literature in at least 3387 dogs (Table 1). PDH is one of the most common endocrine disorders in dogs, with an estimated prevalence of 1 in every 500 dogs (O'Neill et al., 2016). The chronic hypercortisolism results in severe multisystem morbidity, which becomes evident through clinical signs such as polyuria, polydipsia, polyphagia, central obesity, skin and muscle atrophy, hepatomegaly, progressive bilateral alopecia, panting, and systemic hypertension (Galac et al., 2010). In addition to the effects induced by hypercortisolism, the pituitary adenoma can induce space-occupying effects, which can result in neurological signs such as altered behaviour, abnormal posture and gait, and cranial nerve deficits (Menchetti et al., 2019). Several breeds are reported to have an increased prevalence of PDH, including bichon frise, dachshund, Yorkshire terrier, miniature poodles, Irish setter, and basset hound (O'Neill et al., 2016; Hoffman et al., 2018). Corticotroph adenomas have been described with other concurrent endocrine neoplasia in dogs, most often found with adrenal gland tumours (Beatrice et al., 2018). Recently, Van Bokhorst et al. (2019) reported that 5% of all dogs with hypercortisolism have concurrent pituitary and adrenal gland lesions (van Bokhorst et al., 2019).

A recent study examined the pituitary glands from 136 dogs that were collected during routine necropsies and found that 7% of middle-aged and 21% of old dogs had a corticotroph adenoma. Of these dogs, only 1 out of 11 presented with clinical signs of PDH (Polledo et al., 2018). The prevalence of corticotroph adenomas in dogs might therefore be even higher than currently thought. In humans, corticotroph adenomas that do not present with clinical signs of PDH are thought to be related to incomplete processing of the precursor molecule POMC into the biologically active ACTH (1-

39) (Al-Brahim and Asa, 2006). In 1995, Goossens et al. described a dog with a pituitary tumour that had no clinical signs of PDH, but had high circulating POMC levels (Goossens et al., 1995). The more recent study by Benchekroun et al. suggests that POMC processing is altered especially in large pituitary tumours in dogs, and is related to decreased expression of the PC1/3 enzyme (Benchekroun et al., 2018).

The therapeutic management of dogs with PDH has been recently reviewed elsewhere (Sanders et al., 2018). In short, pituitary-targeted treatment options include surgical removal (transsphenoidal hypophysectomy) or radiotherapy. Hypophysectomy has been shown to successfully lower hormone concentrations to below normal values (Meij et al., 1998, 2002). Radiotherapy can be useful to reduce adenoma size, but usually does not achieve complete remission of hypercortisolism (de Fornel et al., 2007; Sellon et al., 2009; Sawada et al., 2018). Because hypophysectomy and radiotherapy are not widely available and include risks, dogs are often treated medically. Medical treatment of dogs with PDH is currently aimed at regulating cortisol levels with the adrenal steroidogenesis inhibitor trilostane (Ramsey, 2010; Sanders et al., 2018). Pituitary-targeted medical treatment options, such as the somatostatin analogue pasireotide (Castillo et al., 2011; Lottati and Bruyette, 2018), or the vitamin A1 metabolite retinoic acid (Castillo et al., 2006), have shown some promise in experimental treatment of dogs with PDH. Pituitary-targeted medical treatment options and combination therapies are therefore interesting avenues for future research.

Corticotroph adenomas were first described in dogs over 80 years ago (Verstraete and Thoonen, 1939), but the reason why these tumours develop with a relatively high prevalence is still unknown. Pituitary adenomas are thought to be monoclonal in origin, suggesting that they develop from a single genetically transformed pituitary cell (Van Wijk et al., 1998; Castillo and Gallelli, 2010). Several candidate genes have been sequenced that could explain corticotroph adenoma formation in dogs, but so far no causative mutations have been identified (Van Wijk et al., 1997; Hanson et al., 2008; Sbiera et al., 2016).

In theory, corticotroph adenoma development could be related to (1) increased positive feedback signals by for example constitutively activate corticotropin-releasing hormone (CRH) receptors; (2) decreased negative feedback signals through glucocorticoid resistance by for example glucocorticoid receptor (GR) deficiency; (3) gain-of-function mutations in proto-oncogenes such as the tyrosine kinase C-MYC; and (4) loss-of-function mutations in tumour suppressor genes such as p27 (Van Wijk et al., 1998; Castillo and Gallelli, 2010). Negative feedback regulation by the GR is in part regulated by two factors called BRG1 and HDAC2, which inhibit POMC expression. Interestingly, approximately 50% of both human and canine corticotroph adenomas lack nuclear expression of BRG1 and HDAC2, suggesting a potential molecular basis for glucocorticoid resistance (Bilodeau et al., 2006). New techniques such as whole genome sequencing are expected to increase our understanding of the molecular pathogenesis of these tumours, which could also help to develop more targeted treatment options.

Cats

In cats, PDH is much less common than in dogs (Feldman and Nelson, 1994). Corticotroph adenomas have been described in at least 126 cats (Table 1), making them the second most commonly reported pituitary tumour type in cats. Corticotroph adenomas that induce PDH are most often detected in middle-aged to elderly cats, without breed or sex predilection. The chronic hypercortisolism can result in abdominal enlargement, polyphagia, skin and muscle wasting, and lethargy (Valentin et al., 2014; Galac and Rosenberg, 2019). Cats with PDH can have extremely fragile skin, and iatrogenic skin tears induced during diagnostic or therapeutic handling are not uncommon (Boland and Barrs, 2017). Cats with PDH do not present with polyuria and polydipsia due to the glucocorticoid excess, but rather due to concurrent diabetes mellitus (Galac and Rosenberg, 2019). Diabetes mellitus resulting from insulin resistance is common in cats with PDH (Boland and Barrs, 2017).

In two cats, a corticotroph adenoma was observed in combination with pancreatic beta cell carcinomas and thyroid C-cell hyperplasia, suggestive of a multiple endocrine neoplasia 1 (MEN-1)-like syndrome (Roccabianca et al., 2006). This clinical picture closely resembled that of two previously described cats that presented with insulin-resistant diabetes mellitus, hypercortisolism, and pancreatic exocrine neoplasia (Kipperman et al., 1992).

Because PDH is less common in cats than in dogs, the therapeutic possibilities have been less well-studied. Just as in dogs, pituitary-targeted treatment options include transsphenoidal hypophysectomy (Meij et al., 2001) and radiotherapy (Mayer et al., 2006). As medical treatment, trilostane can be used to inhibit adrenal steroidogenesis (Galac and Rosenberg, 2019). Trilostane induces clinical improvement in the majority of cats and seems to be well-tolerated overall (Neiger et al., 2004; Mellett Keith et al., 2013; Valentin et al., 2014).

Although both corticotroph and melanotroph adenomas can result in PDH, a specific melanotroph adenoma that did not excessively secrete ACTH was described in a 13-year-old male cat with insulin-resistant diabetes mellitus (Meij et al., 2005). The cat had a ravenous appetite and a dull coat. Endocrine testing showed that there was no evidence of PDH, but basal plasma α-MSH concentrations were highly increased. Computed tomography revealed a pituitary tumour, and after hypophysectomy the clinical signs resolved and the cat no longer required insulin administration. Microscopic examination of the surgical specimen revealed a pituitary adenoma originating from the IL with infiltration into the neural lobe. The adenoma immunostained positive intensely for α-MSH, and only weakly for ACTH (Meij et al., 2005).

Somatotroph adenomas

Somatotroph adenomas are pituitary adenomas from the PIT1 lineage that express GH. Somatotroph adenomas can excessively secrete GH, which results in hypersomatotropism (HS). Chronic HS can induce the clinical syndrome of acromegaly, which is associated with enlargement of cranial features and internal organs (Meij et al., 2010a), but these changes are often subtle and difficult to recognize, or even absent (Lamb et al., 2014; Niessen et al., 2015).

Dogs

Somatotroph adenomas have sporadically been described in dogs (Reusch et al., 2019). Although HS is relatively common in dogs, this is rarely caused by a pituitary tumour. In bitches, HS most often originates from the mammary gland, where excess growth hormone is produced in response to high endogenous progesterone produced during the luteal phase (Selman et al., 1994; Mol et al., 1999).

At least four cases of canine somatotroph adenomas have been reported (Van Keulen et al., 1996; Fracassi et al., 2007; Zublena et al., 2018; Reusch et al., 2019). Additionally, in a recent study that performed IHC on 16 canine pituitary adenomas, one hormonally silent pituitary adenoma stained positive for both ACTH and GH, classifying it as a plurihormonal adenoma (Miller et al., 2018b). Of the four reported dogs with somatotroph adenomas, insulin-

resistant diabetes mellitus was present in three cases (Van Keulen et al., 1996; Zublena et al., 2018; Reusch et al., 2019), and clinical signs associated with acromegaly in three cases (Fracassi et al., 2007; Zublena et al., 2018; Reusch et al., 2019). These clinical signs included enlargement of the head, tongue and paws, thick and redundant skin folds, and widened interdental spaces (Fracassi et al., 2007; Zublena et al., 2018; Reusch et al., 2019).

Cats

Somatotroph adenomas have been reported in at least 393 cats (Table 1), making it the most commonly reported pituitary tumour type in cats. Somatotroph adenomas that induce HS are most often detected in middle-aged to older cats. Although all genders and breeds can be affected, neutered males, Domestic Shorthairs and Maine Coon cats might be more susceptible (Gunn-Moore, 2005; Niessen et al., 2015; Niessen and Scudder, 2019). The GH excess can cause insulin resistance, which can result in diabetes mellitus (Niessen et al., 2007). Recent reports suggest that cats with diabetes mellitus have HS in 18% (Schaefer et al., 2017) to 25% (Niessen et al., 2015) of cases. In the largest study that screened for HS in diabetic cats to date, HS was suspected by the clinician in only 24% of cats that were found to have increased IGF-1 concentrations (Niessen et al., 2015). The current estimation is that 1 in every 800 cats has HS (Niessen and Scudder, 2019). Considering that hundreds of millions of cats live in this world while only 393 cases with somatotroph adenomas have been reported in literature so far, HS seems to be a highly underreported endocrinopathy.

Although cats with HS were previously thought to always be diabetic, recent reports have shown that is not always the case (Fletcher et al., 2016; Connolly et al., 2019). A recent study reported on three cats with HS without concurrent diabetes mellitus (Fletcher et al., 2016). In two of these cats, the pituitary adenomas were examined with IHC. Interestingly, both adenomas showed immunoreactivity for not only GH, but also ACTH and FSH, and in one adenoma also α-MSH, classifying them as plurihormonal adenomas (Fletcher et al., 2016). In addition, of 66 non-diabetic cats with hypertrophic cardiomyopathy, four cats (6%) were reported to have HS (Connolly et al., 2019). Clinical conditions other than diabetes mellitus that can raise suspicion of HS include hypertrophic cardiomyopathy-like disease, snoring or stertor starting later in life, and abnormalities of the central nervous system (Niessen and Scudder, 2019). Screening for HS in non-diabetic cats to better estimate the overall prevalence of cats with HS would be an interesting avenue for future research.

Treatment options for HS in cats include transsphenoidal hypophysectomy, radiotherapy, and medical treatment (Meij et al., 2010a). Hypophysectomy is able to cure cats with HS, of which a high percentage also achieves diabetic remission (Meij et al., 2010b; Kenny et al., 2016; Neilson et al., 2019; van Bokhorst et al., 2020). Radiotherapy can reduce or resolve the neurological signs by reducing the tumor size. Remission of HS or diabetes mellitus is, however, often not achieved (Niessen and Scudder, 2019). For pituitary-targeted medical treatment options, dopamine agonists and somatostatin analogues have been studied (Scudder et al., 2015, 2020; Gostelow et al., 2017). Among the somatostatin receptors (SSTR) and D_2 dopamine receptor (DRD2), SSTR1, -2, -5, and DRD2 were expressed in pituitary glands of cats with HS (Scudder et al., 2019). The dopamine agonist cabergoline gave unsatisfactory results (Scudder et al., 2020), while the multiligand somatostatin analogue pasireotide has been shown to decrease IGF-1 concentration and increase insulin sensitivity in cats with HS and concurrent diabetes mellitus (Scudder et al., 2015; Gostelow et al., 2017).

The cause of the relatively high frequency of somatotroph adenoma formation in cats is not clear, but there has been some speculation on whether organohalogenated chemicals (OHCs) play a role. Cats with HS were found to have higher plasma OHC concentrations than cats with diabetes mellitus without HS and healthy cats (Dirtu et al., 2013). These OHCs share some chemical characteristics with oestrogens, which could potentially induce pituitary adenoma formation (Niessen and Scudder, 2019). In a rat somatolactotroph cell line, OHCs were recently reported to increase cell proliferation in a concentration-dependent manner (Ringrose et al., 2020). In addition, the aryl-hydrocarbon-receptor interacting protein (*AIP*) gene was found to have a single nonsynonymous single-nucleotide polymorphism (SNP) in 20% of studied cats with acromegaly (Scudder et al., 2017). This SNP potentially affects the function of the AIP protein, which is thought to be a tumour suppressor, and can modulate the response to oestrogens, androgens, and xenobiotics. The latter function is especially interesting, since this might be related to the aforementioned OHCs (Scudder et al., 2017). Environmental and genetic factors therefore potentially play a role in feline somatotroph adenoma formation.

Lactotroph adenomas

Lactotroph adenomas, also referred as prolactinomas, are pituitary adenomas from the PIT1 lineage that express prolactin. In humans, lactotroph adenomas represent 30–50% of all pituitary adenomas, which makes them the most common type of functional adenomas (Mete and Lopes, 2017). In contrast, only one lactotroph adenoma has been described in a dog (Cosio et al., 2017), and none in cats.

Dogs

A lactrotroph adenoma that excessively secreted prolactin has been described in one case report in a 12-year-old intact male Yorkshire Terrier (Cosio et al., 2017). Clinical signs in this dog included intermittent anorexia, mammary gland swelling, and galactorrhea. Serum prolactin concentration was highly increased, and computed tomography (CT) revealed an enlarged pituitary gland. In addition, this dog had a prostate carcinoma. Treatment with cabergoline, a dopamine agonist, completely resolved the galactorrhea and greatly reduced the serum prolactin concentration, which both reappeared when the treatment was suspended. Postmortem examination revealed a pituitary adenoma that showed immunoreactivity for prolactin, but not for ACTH, α-MSH, or GH, thereby confirming the diagnosis of a lactotroph adenoma (Cosio et al., 2017).

Thyrotroph adenomas

Thyrotroph adenomas are pituitary adenomas from the PIT1 lineage that express TSH. In humans, thyrotroph adenomas account for approximately 1% of pituitary adenomas (Faltermeier et al., 2019). Thyrotroph adenomas have not been described in dogs or cats. One case report describes a dog with a corticotroph adenoma and concurrent thyrotroph hyperplasia, but the latter was probably a consequence of concurrent primary hypothyroidism (Teshima et al., 2009a).

Gonadotroph adenomas

Gonadotroph adenomas are pituitary adenomas from the SF-1 lineage that express LH and/or FSH. In humans, gonadotroph adenomas account for 15–40% of pituitary adenomas, but the vast majority are hormonally silent (Faltermeier et al., 2019). Gonadotroph adenomas have not been described in dogs and cats. However, because these tumours can be hormonally silent and

immunostaining for FSH or LH is not routinely performed, their numbers may be underestimated.

Plurihormonal and double adenomas

A plurihormonal adenoma is a single adenoma that expresses multiple hormones, while a double adenoma consists of two separate adenomas within one pituitary gland. In humans, adenomas that secrete GH in combination with PRL or TSH are relatively common, since all three hormones require the same transcription factor (PIT1). True plurihormonal adenomas, meaning adenomas that express hormones which require different transcription factors, are rare in humans (Al-Brahim and Asa, 2006).

In dogs, two cases with plurihormonal adenomas have been reported: one expressing ACTH and GH (Miller et al., 2018b), and one expressing ACTH, PRL and LH (Mendez et al., 1998). In cats, three cases with plurihormonal adenomas have been reported: two expressing GH, ACTH and FSH (one with additional α-MSH) (Fletcher et al., 2016), and one expressing ACTH, α-MSH and GH (Cross et al., 2012). In addition, two cats have been described that had two separate adenomas within one pituitary gland: one with a somatotroph and a corticotroph adenoma (Meij et al., 2004), and one with a somatotroph and a plurihormonal adenoma (expressing ACTH, α-MSH, FSH) (Sharman et al., 2013). Interestingly, most of the described canine and feline plurihormonal adenomas require a cross-over of transcription factors. However, antibodies can be raised against the α-subunit of a hormone, which is expressed by cells of both the PIT1 and SF-1 lineage (Al-Brahim and Asa, 2006). Additionally, human corticotroph adenomas have been described that express both ACTH and α-subunit, but no other hormones (Suzuki et al., 2008). Therefore, depending on which antibodies were used, some of these cases might be explained by non-specific antibody cross-reactivity to the α-subunit (Al-Brahim and Asa, 2006).

Null cell adenomas

A null cell adenoma is a pituitary adenoma that expresses neither hormones nor lineage-specific transcription factors. In humans, null cell adenomas account for less than 1% of all pituitary adenomas (Faltermeier et al., 2019). In dogs, one pituitary tumour has been described that was negative for ACTH, α-MSH, GH and PRL (Polledo et al., 2018). The authors did not report staining for LH and FSH. In this case, IHC for transcription factor expression would have been interesting to determine whether this concerned a null cell adenoma or a lineage-specific adenoma. Null cell adenomas probably remain undetected in dogs and cats because pituitary surgical specimens are not routinely stained for a complete panel of hormones or transcription factors.

Other pituitary pathologies

Apart from tumours of the adenohypophysis, other masses that can develop in this region include craniopharyngioma, Rathke's cleft cyst, pituicytoma, secondary neoplasms, hypophysitis, or hyperplasia (Kleinschmidt-DeMasters, 2016; Miller et al., 2018a).

Craniopharyngiomas are rare, generally benign epithelial tumours in the (supra)sellar region that are presumably derived from early pituitary progenitor cells in Rathke's pouch (Desiderio et al., 2020). Craniopharyngiomas have been described in at least eight dogs (Saunders and Rickard, 1952; Neer and Reavis, 1983; Hawkins et al., 1985; Eckersley et al., 1991; Rissi, 2015; Miller et al., 2018a), and two cats (Nagata et al., 2005).

Rathke's cleft cysts, also referred to as craniopharyngeal duct cysts, are non-neoplastic cysts that arise from embryological remnants of Rathke's pouch. Although Rathke's cleft cysts are common incidental lesions in dogs, they are usually not associated with clinical disease (Miller et al., 2018a). When clinical disease does occur, this can be related to pituitary dysfunction by compression of adjacent tissue (Hamann et al., 1999). A Rathke's cleft cyst has been reported in one cat, in which it was hypothesized to have induced the syndrome of inappropriate antidiuretic hormone secretion (DeMonaco et al., 2014).

A pituicytoma is a tumour that arises from pituicytes in the neurohypophysis. A pituicytoma has been reported in one dog (Miller et al., 2018a), and not in cats.

Secondary neoplasms are related to metastases or local extension of other tumour types. In a recent large case series of canine pituitary pathologies, secondary neoplasms included metastatic carcinomas (urothelial, nasal, and unknown carcinomas), lymphomas, metastatic melanomas, local extension of ependymomas, oligodendroglial gliomatosis, and meningioma (Miller et al., 2018a).

Hypophysitis can be a primary inflammation of the pituitary gland, or secondary to an encephalitis or a systemic immune-mediates disease. Hypophysitis has been described in seven dogs (Wolfesberger et al., 2011; Meij et al., 2012; Polledo et al., 2017; Rzechorzek et al., 2017; Miller et al., 2018a) and one cat (Rudinsky et al., 2015). When the inflammatory process severely affects pituitary cells of either the adeno- or neurohypophysis, either directly or through mass-occupying effects, this can result in pituitary dysfunction (Meij et al., 2012; Rudinsky et al., 2015).

Pituitary hyperplasia is characterized by increased proliferation of a specific pituitary cell type, which can be diffuse, focal, or nodular. Pituitary hyperplasia is usually secondary to either increased stimulatory or decreased inhibitory extrinsic signals (Melmed, 2003). In healthy dogs, treatment with trilostane resulted in hyperplasia of the corticotroph pituitary cells, as a consequence of decreased negative feedback (Teshima et al., 2009b). Although this has not been studied in dogs with PDH, pituitary adenoma growth could potentially be accelerated when using adrenal-targeted treatment options, similar to Nelson's syndrome in humans (Teshima et al., 2009b). In dogs with induced primary hypothyroidism, the reduced negative feedback resulted in thyrotroph cell hyperplasia. In addition, cells were detected that stained positive for both GH and TSH, indicating transdifferentiation of somatotroph cells to thyrosomatotroph cells (Diaz-Espiñeira et al., 2008). In 21 cats with HS, almost half of the pituitary glands showed hyperplastic changes (Scudder et al., 2019). This percentage was greater than expected, and potentially indicates that hyperplastic changes can precede somatotroph adenoma formation (Scudder et al., 2019). Pituitary hyperplasia can be distinguished from pituitary adenoma with reticulin staining, which will show intact acinar structures increased in size in case of hyperplasia, and a loss of reticulin fibres in case of adenoma (Polledo et al., 2018; Scudder et al., 2019).

Conclusions

Pituitary tumours are relatively common in dogs and are being increasingly recognized in cats. In dogs, the most common pituitary tumour is the corticotroph adenoma. In cats, the most common pituitary tumour is the somatotroph adenoma, followed by the corticotroph adenoma. Hormonally silent adenomas are likely underdiagnosed since they lack a hormonal syndrome. The tools that are used to classify pituitary tumours in humans, in particular IHC for lineage-specific transcription factors, could be useful to classify canine and feline pituitary tumours of unknown origin. Future studies, including complete hormonal panel staining of adenomas, are required to better understand the full scope of adenomas in dogs and cats and to determine whether certain

adenoma subtypes behave more aggressively than others. Currently, the mechanisms that underlie pituitary tumorigenesis in dogs and cats are still largely unknown. A better understanding of the molecular background of these tumours could potentially help to identify improved pituitary-targeted therapeutics.

Conflict of interest

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.tvjl.2021.105623.

References

Al-Brahim, N.Y.Y., Asa, S.L., 2006. My approach to pathology of the pituitary gland. Journal of Clinical Pathology 59, 1245–1253.

Beatrice, L., Boretti, F.S., Sieber-Ruckstuhl, N.S., Mueller, C., Kümmerle-Fraune, C., Hilbe, M., Grest, P., Reusch, C.E., 2018. Concurrent endocrine neoplasias in dogs and cats: a retrospective study (2004–2014). The Veterinary Record 182, 323.

Benchekroun, G., de Fornel-Thibaud, P., Rosenberg, D., 2018. Proopiomelanocortin processing and prohormone convertase 1 level in dogs with pituitary corticotroph tumors. Domestic Animal Endocrinology 62, 83–87.

Bicknell, A.B., 2008. The tissue-specific processing of pro-opiomelanocortin. Journal of Neuroendocrinology 20, 692–699.

Bilodeau, S., Vallette-Kasic, S., Gauthier, Y., Figarella-Branger, D., Brue, T., Berthelet, F., Lacroix, A., Batista, D., Stratakis, C., Hanson, J., Meij, B., Drouin, J., 2006. Role of Brg1 and HDAC2 in GR trans-repression of the pituitary POMC gene and misexpression in Cushing disease. Genes and Development 20, 2871–2886.

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.

Castillo, V.A., Gallelli, M.F., 2010. Corticotroph adenoma in the dog: pathogenesis and new therapeutic possibilities. Research in Veterinary Science 88, 26–32.

Castillo, V., Giacomini, D., Páez-Pereda, M., Stalla, J., Labeur, M., Theodoropoulou, M., Holsboer, F., Grossman, A.B., Stalla, G.K., Arzt, E., 2006. Retinoic acid as a novel medical therapy for Cushing's disease in dogs. Endocrinology 147, 4438–4444.

Castillo, V., Theodoropoulou, M., Stalla, J., Gallelli, M.F., Cabrera-Blatter, M.F., Haedo, M.R., Labeur, M., Schmid, H.A., Stalla, G.K., Arzt, E., 2011. Effect of SOM230 (Pasireotide) on corticotropic cells: action in dogs with Cushing's disease. Neuroendocrinology 94, 124–136.

Connolly, D.J., Payne, J.R., Borgeat, K., Church, D.B., Steele, M., Coss, P., Niessen, S.J.M., 2019. [Conference presentation abstract] Prevalence of hypersomatotropism in non-diabetic cats with left ventricular hypertrophy — a silent and curable phenocopy for hypertrophic cardiomyopathy. Research Communications of the 28th ECVIM-CA Congress. Journal of Veterinary Internal Medicine 33.

Cosio, C., Sartori, E., Garatti, M., Luccardini, L., Grinwis, G.C.M., Kooistra, H.S., Fracassi, F., 2017. Prolactinoma in a dog. Veterinary Pathology 54, 972–976.

Cox, B., Roose, H., Vennekens, A., Vankelecom, H., 2017. Pituitary stem cell regulation: who is pulling the strings? Journal of Endocrinology 234, R135–R158.

Cross, E., Moreland, R., Wallack, S., 2012. Feline pituitary-dependent hyperadrenocorticism and insulin resistance due to a plurihormonal adenoma. Topics in Companion Animal Medicine 27, 8–20.

Davis, S.W., Ellsworth, B.S., Peréz Millan, M.I., Gergics, P., Schade, V., Foyouzi, N., Brinkmeier, M.L., Mortensen, A.H., Camper, S.A., 2013. Pituitary gland development and disease: from stem cell to hormone production. Current Topics in Developmental Biology, , pp. 1–47.

de Fornel, P., Delisle, F., Devauchelle, P., Rosenberg, D., 2007. Effects of radiotherapy on pituitary corticotroph macrotumors in dogs: a retrospective study of 12 cases. Canadian Veterinary Journal 48, 481–486.

DeMonaco, S.M., Koch, M.W., Southard, T.L., 2014. Syndrome of inappropriate antidiuretic hormone secretion in a cat with a putative Rathke's cleft cyst. Journal of Feline Medicine and Surgery 16, 1010–1015.

Desiderio, C., Rossetti, D.V., Castagnola, M., Massimi, L., Tamburrini, G., 2020. Adamantinomatous craniopharyngioma: advances in proteomic research. Child's Nervous System doi:http://dx.doi.org/10.1007/s00381-020-04750-z Online ahead of print.

Diaz-Espiñeira, M.M., Mol, J.A., van den Ingh, T.S.G.A.M., van der Vlugt-Meijer, R.H., Rijnberk, A., Kooistra, H.S., 2008. Functional and morphological changes in the adenohypophysis of dogs with induced primary hypothyroidism: loss of TSH hypersecretion, hypersomatotropism, hypoprolactinemia, and pituitary enlargement with transdifferentiation. Domestic Animal Endocrinology 35, 98–111.

Dirtu, A.C., Niessen, S.J.M., Jorens, P.G., Covaci, A., 2013. Organohalogenated contaminants in domestic cats' plasma in relation to spontaneous acromegaly and type 2 diabetes mellitus: a clue for endocrine disruption in humans? Environment International 57–58, 60–67.

Eckersley, G.N., Geel, J.K., Kriek, N.P., 1991. A craniopharyngioma in a seven-year-old dog. Journal of the South African Veterinary Association 62, 65–67.

Faltermeier, C.M., Magill, S.T., Blevins, L.S., Aghi, M.K., 2019. Molecular biology of pituitary adenomas. Neurosurgery Clinics of North America 30, 391–400.

Feldman, E.C., Nelson, R.W., 1994. Comparative aspects of Cushing's syndrome in dogs and cats. Endocrinology and Metabolism Clinics of North America 23, 671–691.

Fletcher, J.M., Scudder, C.J., Kiupel, M., Pipe-Martin, H.N., Kenny, P.J., Mantis, P., Fenn, J., Smith, K., Blair, R.V., Granger, L.A., Niessen, S.J.M., 2016. Hypersomatotropism in 3 cats without concurrent diabetes mellitus. Journal of Veterinary Internal Medicine 30, 1216–1221.

Fracassi, F., Gandini, G., Diana, A., Preziosi, R., van den Ingh, T.S.G.A.M., Famigli-Bergamini, P., Kooistra, H.S., 2007. Acromegaly due to a somatroph adenoma in a dog. Domestic Animal Endocrinology 32, 43–54.

Galac, S., Rosenberg, D., 2019. Cushing's syndrome (hypercortisolism). In: Feldman, E.C., Fracassi, F., Peterson, M.E. (Eds.), The Handbook of Feline Endocrinology. Servet Publishing, pp. 363–380.

Galac, S., Reusch, C.E., Kooistra, H.S., Rijnberk, A., 2010. Adrenals. In: Rijnberk, A., Kooistra, H.S. (Eds.), Clinical Endocrinology of Dogs and Cats. Schlütersche, pp. 93–154.

Goossens, M.M.C., Rijnberk, A., Mol, J.A., Wolfswinkel, J., Voorhout, G., 1995. Central diabetes insipidus in a dog with a pro-opiomelanocortin-producing pituitary tumor causing hyperadrenocorticism. Journal of Veterinary Internal Medicine 9, 361–365.

Gostelow, R., Scudder, C., Keyte, S., Forcada, Y., Fowkes, R.C., Schmid, H.A., Church, D. B., Niessen, S.J.M., 2017. Pasireotide long-acting release treatment for diabetic cats with underlying hypersomatotropism. Journal of Veterinary Internal Medicine 31, 355–364.

Gunn-Moore, D., 2005. Feline endocrinopathies. Veterinary Clinics of North America: Small Animal Practice 35, 171–210.

Hamann, F., Kooistra, H.S., Mol, J.A., Gottschalk, S., Bartels, T., Rijnberk, A., 1999. Pituitary function and morphology in two German shepherd dogs with congenital dwarfism. Veterinary Record 144, 644–646.

Hanson, J.M., Mol, J.A., Leegwater, P.A.J., Bilodeau, S., Drouin, J., Meij, B.P., 2008. Expression and mutation analysis of Tpit in the canine pituitary gland and corticotroph adenomas. Domestic Animal Endocrinology 34, 217–222.

Hawkins, K.L., Diters, R.W., McGrath, J.T., 1985. Craniopharyngioma in a dog. Journal of Comparative Pathology 95, 469–474.

Hoffman, J.M., Lourenço, B.N., Promislow, D.E.L., Creevy, K.E., 2018. Canine hyperadrenocorticism associations with signalment, selected comorbidities and mortality within North American veterinary teaching hospitals. Journal of Small Animal Practice 59, 681–690.

Inoshita, N., Nishioka, H., 2018. The 2017 WHO classification of pituitary adenoma: overview and comments. Brain Tumor Pathology 35, 51–56.

Jagannathan, J., Kanter, A.S., Sheehan, J.P., Jane, J.A., Laws, E.R., 2007. Benign brain tumors: sellar/parasellar tumors. Neurologic Clinics 25, 1231–1249.

Kenny, P.J., Scudder, C.J., Keyte, S.V., Swann, J.W., Fowkes, R.C., Church, D.B., Forcada, Y., Niessen, S.J.M., 2016. [Conference presentation abstract] experiences of a newly established hypophysectomy clinic for treatment of feline hypersomatotrophism. Research communications of the 25th ECVIM-CA Congress. Journal of Veterinary Internal Medicine 30.

Kipperman, B.S., Nelson, R.W., Griffey, S.M., Feldman, E.C., 1992. Diabetes mellitus and exocrine pancreatic neoplasia in two cats with hyperadrenocorticism. Journal of the American Animal Hospital Association 28, 415–418.

Kleinschmidt-DeMasters, B.K., 2016. Histological features of pituitary adenomas and sellar region masses. Current Opinion in Endocrinology, Diabetes and Obesity 23, 476–484.

Lamb, C.R., Ciasca, T.C., Mantis, P., Forcada, Y., Potter, M., Church, D.B., Niessen, S.J., 2014. Computed tomographic signs of acromegaly in 68 diabetic cats with hypersomatotropism. Journal of Feline Medicine and Surgery 16, 99–108.

Lottati, M., Bruyette, D.S., 2018. Outcomes of the addition of pasireotide to tranditional adrenal-directed treatment for dogs with pituitary-dependent hyperadrenocorticism secondary to macroadenoma: 9 cases (2013–2015). Journal of the American Veterinary Medical Association 252, 1403–1408.

Manojlovic-Gacic, E., Bollerslev, J., Casar-Borota, O., 2019. Invited review: pathology of pituitary neuroendocrine tumours: present status, modern diagnostic approach, controversies and future perspectives from a neuropathological and clinical standpoint. Neuropathology and Applied Neurobiology 46, 89–110.

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., Van Den Ingh, T.S.G.A.M., Hazewinkel, H.A.W., Teske, E., Rijnberk, A., 1998. Results of transsphenoidal hypophysectomy in 52 dogs with pituitary-dependent hyperadrenocorticism. Veterinary Surgery 27, 246–261.

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

Meij, B., Voorhout, G., Rijnberk, A., 2002. Progress in transsphenoidal hypophysectomy for treatment of pituitary-dependent hyperadrenocorticism in dogs and cats. Molecular and Cellular Endocrinology 197.

Meij, B.P., van der Vlugt-Meijer, R.H., van den Ingh, T.S.G.A.M., Rijnberk, A., 2004. Somatotroph and corticotroph pituitary adenoma (double adenoma) in a cat

with diabetes mellitus and hyperadrenocorticism. Journal of Comparative Pathology 130, 209–215.
Meij, B.P., Van Der Vlugt-Meijer, R.H., Van Den Ingh, T.S.G.A.M., Flik, G., Rijnberk, A., 2005. Melanotroph pituitary adenoma in a cat with diabetes mellitus. Veterinary Pathology 42, 92–97.
Meij, B.P., Kooistra, H.S., Rijnberk, A., 2010a. Hypothalamus-pituitary system. In: Rijnberk, A., Kooistra, H.S. (Eds.), Clinical Endocrinology of Dogs and Cats. Schlütersche, pp. 13–54.
Meij, B.P., Auriemma, E., Grinwis, G., Buijtels, J.J.C.W.M., Kooistra, H.S., 2010b. Successful treatment of acromegaly in a diabetic cat with transsphenoidal hypophysectomy. Journal of Feline Medicine and Surgery 12, 406–410.
Meij, B.P., Voorhout, G., Gerritsen, R.J., Grinwis, G.C.M., Ijzer, J., 2012. Lymphocytic hypophysitis in a dog with diabetes insipidus. Journal of Comparative Pathology 147, 503–507.
Mellett Keith, A.M., Bruyette, D., Stanley, S., 2013. Trilostane therapy for treatment of spontaneous hyperadrenocorticism in cats: 15 cases (2004–2012). Journal of Veterinary Internal Medicine 27, 1471–1477.
Melmed, S., 2003. Mechanisms for pituitary tumorigenesis: the plastic pituitary. Journal of Clinical Investigation 112, 1603–1618.
Menchetti, M., De Risio, L., Galli, G., Cherubini, G.B., Corlazzoli, D., Baroni, M., Gandini, G., 2019. Neurological abnormalities in 97 dogs with detectable pituitary masses. Veterinary Quarterly 39, 57–64.
Mendez, A., Martin de las Mulas, J., Bautista, M.J., Chacon, F., Millan, Y., Fondevila, D., Pumarola, M., 1998. Comparative immunohistochemical study of stellate cells in normal canine and equine adenohypophyses and in pituitary tumours. Journal of Comparative Pathology 118, 29–40.
Mete, O., Lopes, M.B., 2017. Overview of the 2017 WHO Classification of Pituitary Tumors. Endocrine Pathology 28, 228–243.
Miller, M.A., Bruyette, D.S., Scott-Moncrieff, J.C., Owen, T.J., Ramos-Vara, J.A., Weng, H.Y., Vanderpool, A.L., Chen, A.V., Martin, L.G., DuSold, D.M., Jahan, S., 2018a. Histopathologic findings in canine pituitary glands. Veterinary Pathology 55, 871–879.
Miller, M.A., Owen, T.J., Bruyette, D.S., Scott-Moncrieff, J.C., Ramos-Vara, J.A., Weng, H.Y., Chen, A.V., Martin, L.G., DuSold, D.M., 2018b. Immunohistochemical evaluation of canine pituitary adenomas obtained by transsphenoidal hypophysectomy. Veterinary Pathology 55, 889–895.
Mol, J.A., Lantinga-van Leeuwen, I.S., Selman, P.J., Oosterlaken-Dijksterhuis, M.A., Schalken, J.A., Rijnberk, A., Mol, J.A., van Garderen, E., Schalken, J.A., 1999. Mammary growth hormone and tumorigenesis — lessons from the dog. Veterinary Quarterly 21, 111–115.
Nagata, T., Nakayama, H., Uchida, K., Uetsuka, K., Yasoshima, A., Yasunaga, S., Masuda, K., Tsujimoto, H., Kuwajima, E., Nishimura, R., Sasaki, N., Doi, K., 2005. Two cases of feline malignant craniopharyngioma. Veterinary Pathology 42, 663–665.
Neer, T.M., Reavis, D.U., 1983. Craniopharyngioma and associated central diabetes insipidus and hypothyroidism in a dog. Journal of the American Veterinary Medical Association 182, 519–520.
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.
Neilson, D.M., Viscasillas, J., Alibhai, H.I.K., Kenny, P.J., Niessen, S.J.M., Sanchis-Mora, S., 2019. Anaesthetic management and complications during hypophysectomy in 37 cats with acromegaly. Journal of Feline Medicine and Surgery 21, 347–352.
Niessen, S.J.M., Scudder, C.J., 2019. GH excess: acromegaly (hypersomatotropism). In: Feldman, E.C., Fracassi, F., Peterson, M.E. (Eds.), The Handbook of Feline Endocrinology. Servet Publishing, pp. 9–26.
Niessen, S.J.M., Petrie, G., Gaudiano, F., Khalid, M., Smyth, J.B.A., Mahoney, P., Church, D.B., 2007. Feline acromegaly: an underdiagnosed endocrinopathy? Journal of Veterinary Internal Medicine 21, 899–905.
Niessen, S.J.M., Forcada, Y., Mantis, P., Lamb, C.R., Harrington, N., Fowkes, R., Korbonits, M., Smith, K., Church, D.B., 2015. Studying cat (Felis catus) diabetes: beware of the acromegalic imposter. PLoS One 10.
O'Neill, D.G., Scudder, C., Faire, J.M., Church, D.B., McGreevy, P.D., Thomson, P.C., Brodbelt, D.C., 2016. Epidemiology of hyperadrenocorticism among 210,824 dogs attending primary-care veterinary practices in the UK from 2009 to 2014. Journal of Small Animal Practice 57, 365–373.
Ostrom, Q.T., Gittleman, H., Truitt, G., Boscia, A., Kruchko, C., Barnholtz-Sloan, J.S., 2018. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011–2015. NeuroOncology 20, iv1–iv86.
Polledo, L., Oliveira, M., Adamany, J., Graham, P., Baiker, K., 2017. Hypophysitis, panhypopituitarism, and hypothalamitis in a Scottish terrier dog. Journal of Veterinary Internal Medicine 31, 1527–1532.
Polledo, L., Grinwis, G.C.M., Graham, P., Dunning, M., Baiker, K., 2018. Pathological findings in the pituitary glands of dogs and cats. Veterinary Pathology 55, 880–888.
Ramsey, I.K., 2010. Trilostane in dogs. Veterinary Clinics of North America: Small Animal Practice 40, 269–283.
Reusch, C.E., Burkhardt, W.A., Meier, V.S., Rohrer Bley, C., Riond, B., Dennler, M., Boretti, F.S., Sieber-Ruckstuhl, N.S., 2019. Acromegaly due to a pituitary tumor in a dog — diagnosis, therapy and long-term follow-up. Schweizer Archiv fur Tierheilkunde 161, 319–327.
Ringrose, S., Grammatopoulos, K., Welch, N., Simbi, B., Niessen, S.J., McGonnell, I.M., Scudder, C.J., Fowkes, R.C., 2020. SAT-723 Effects of organohalogenated endocrine disrupting chemicals on cell proliferation and gene expression in GH3 somatolactotropes. Journal of the Endocrine Society 4.
Rissi, D.R., 2015. A retrospective study of skull base neoplasia in 42 dogs. Journal of Veterinary Diagnostic Investigation 27, 743–748.
Rizzoti, K., Lovell-Badge, R., 2005. Early development of the pituitary gland: induction and shaping of Rathke's pouch. Reviews in Endocrine and Metabolic Disorders 6, 161–172.
Roccabianca, P., Rondena, M., Paltrinieri, S., Pocacqua, V., Scarpa, P., Faverzani, S., Scanziani, E., Caniatti, M., 2006. Multiple endocrine neoplasia type-I-like syndrome in two cats. Veterinary Pathology 43, 345–352.
Rudinsky, A.J., Clark, E.S., Russell, D.S., Gilor, C., 2015. Adrenal insufficiency secondary to lymphocytic panhypophysitis in a cat. Australian Veterinary Journal 93, 327–331.
Rzechorzek, N.M., Liuti, T., Stalin, C., Marioni-Henry, K., 2017. Restored vision in a young dog following corticosteroid treatment of presumptive hypophysitis. BMC Veterinary Research 13, 63.
Sanders, K., Kooistra, H.S., Galac, S., 2018. Treating canine Cushing's syndrome: current options and future prospects. Veterinary Journal 241, 42–51.
Saunders, L.Z., Rickard, C.G., 1952. Craniopharyngioma in a dog with apparent adiposogenital syndrome and diabetes insipidus. The Cornell Veterinarian 42, 490–495.
Sawada, H., Mori, A., Lee, P., Sugihara, S., Oda, H., Sako, T., 2018. Pituitary size alteration and adverse effects of radiation therapy performed in 9 dogs with pituitary-dependent hypercortisolism. Research in Veterinary Science 118, 19–26.
Sbiera, S., Tryfonidou, M.A., Weigand, I., Grinwis, G.C.M., Broeckx, B., Herterich, S., Allolio, B., Deutschbein, T., Fassnacht, M., Meij, B.P., 2016. Lack of ubiquitin specific protease 8 (USP8) mutations in canine corticotroph pituitary adenomas. PLoS One 11.
Schaefer, S., Kooistra, H.S., Riond, B., Suchodolski, J.S., Steiner, J.M., Prins, M., Zini, E., Reusch, C.E., 2017. Evaluation of insulin-like growth factor-1, total thyroxine, feline pancreas-specific lipase and urinary corticoid-to-creatinine ratio in cats with diabetes mellitus in Switzerland and the Netherlands. Journal of Feline Medicine and Surgery 19, 888–896.
Scudder, C.J., Gostelow, R., Forcada, Y., Schmid, H.A., Church, D., Niessen, S.J.M., 2015. Pasireotide for the medical management of feline hypersomatotropism. Journal of Veterinary Internal Medicine 29, 1074–1080.
Scudder, C.J., Niessen, S.J., Catchpole, B., Fowkes, R.C., Church, D.B., Forcada, Y., 2017. Feline hypersomatotropism and acromegaly tumorigenesis: a potential role for the AIP gene. Domestic Animal Endocrinology 59, 134–139.
Scudder, C.J., Mirczuk, S.M., Richardson, K.M., Crossley, V.J., Regan, J.T.C., Gostelow, R., Forcada, Y., Hazuchova, K., Harrington, N., McGonnell, I.M., Church, D.B., Kenny, P.J., Korbonits, M., Fowkes, R.C., Niessen, S.J.M., 2019. Pituitary pathology and gene expression in acromegalic cats. Journal of the Endocrine Society 3, 181–200.
Scudder, C.J., Hazuchova, K., Gostelow, R., Church, D.B., Forcada, Y., Fowkes, R.C., Niessen, S.J.M., 2020. Pilot study assessing the use of cabergoline for the treatment of cats with hypersomatotropism and diabetes mellitus. Journal of Feline Medicine and Surgery 23, 131–137.
Sellon, R.K., Fidel, J., Houston, R., Gavin, P.R., 2009. Linear-accelerator-based modified radiosurgical treatment of pituitary tumors in cats: 11 cases (1997–2008). Journal of Veterinary Internal Medicine 23, 1038–1044.
Selman, P.J., Mol, J.A., Rutteman, G.R., Van Garderen, E., Rijnberk, A., 1994. Progestin-induced growth hormone excess in the dog originates in the mammary gland. Endocrinology 134, 287–292.
Sharman, M., FitzGerald, L., Kiupel, M., 2013. Concurrent somatotroph and plurihormonal pituitary adenomas in a cat. Journal of Feline Medicine and Surgery 15, 945–952.
Snyder, J.M., Shofer, F.S., Van Winkle, T.J., Massicotte, C., 2006. Canine intracranial primary neoplasia: 173 cases (1986–2003). Journal of Veterinary Internal Medicine 20, 669–675.
Snyder, M., Lipitz, L., Skorupski, K.A., Shofer, F.S., Van Winkle, T.J., 2008. Secondary intracranial neoplasia in the dog: 177 cases (1986–2003). Journal of Veterinary Internal Medicine 22, 172–177.
Suzuki, M., Egashira, N., Kajiya, H., Minematsu, T., Takekoshi, S., Tahara, S., Sanno, N., Teramoto, A., Osamura, R.Y., 2008. ACTH and α-subunit are co-expressed in rare human pituitary corticotroph cell adenomas proposed to originate from ACTH-committed early pituitary progenitor cells. Endocrine Pathology 19, 17–26.
Teshima, T., Hara, Y., Shigihara, K., Takehoshi, S., Nezu, Y., Harada, Y., Yogo, T., Teramoto, A., Osamura, R., Tagawa, M., 2009a. Coexistence of corticotroph adenoma and thyrotroph hyperplasia in a dog. Journal of Veterinary Medical Science 71, 93–98.
Teshima, T., Hara, Y., Takekoshi, S., Nezu, Y., Harada, Y., Yogo, T., Teramoto, A., Osamura, R.Y., Tagawa, M., 2009b. Trilostane-induced inhibition of cortisol secretion results in reduced negative feedback at the hypothalamic-pituitary axis. Domestic Animal Endocrinology 36, 32–44.
Troxel, M.T., Vite, C.H., Van Winkle, T.J., Newton, A.L., Tiches, D., Dayrell-Hart, B., Kapatkin, A.S., Shofer, F.S., Steinberg, S.A., 2003. Feline intracranial neoplasia: retrospective review of 160 cases (1985–2001). Journal of Veterinary Internal Medicine 17, 850–859.
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.
van Bokhorst, K.L., Kooistra, H.S., Boroffka, S.A.E.B., Galac, S., 2019. Concurrent pituitary and adrenocortical lesions on computed tomography imaging in dogs with spontaneous hypercortisolism. Journal of Veterinary Internal Medicine 33, 72–78.

van Bokhorst, K.L., Galac, S., Kooistra, H.S., Valtolina, C., Meij, B.P., 2020. [Conference presentation abstract] Hypophysectomy as successful treatment of feline hypersomatotropism: a case series of 25 cats. Research Communications of the 30th ECVIM-CA Online Congress. Journal of Veterinary Internal Medicine 34.

Van Keulen, L.J.M., Wesdorp, J.L., Kooistra, H.S., 1996. Diabetes mellitus in a dog with a growth hormone-producing acidophilic adenoma of the adenohypophysis. Veterinary Pathology 33, 451–453.

Van Wijk, P.A., Rijnberk, A., Croughs, R.J.M., Meij, B.P., Van Leeuwen, I.S., Sprang, E.P. M., Mol, J.A., 1997. Molecular screening for somatic mutations in corticotropic adenomas of dogs with pituitary-dependent hyperadrenocorticism. Journal of Endocrinological Investigation 20, 1–7.

Van Wijk, P.A., Rijnberk, A., Croughs, R.J.M., Meij, B.P., Mol, J.A., 1998. Effects of corticotrophin-releasing hormone, vasopressin and insulin-like growth factor-I on proliferation of and adrenocorticotrophic hormone secretion by canine corticotrophic adenoma cells in vitro. European Journal of Endocrinology 138, 309–315.

Vankelecom, H., Roose, H., 2017. The stem cell connection of pituitary tumors. Frontiers in Endocrinology 8.

Verstraete, A., Thoonen, J., 1939. Twee nieuwe gevallen van hypophysaire stoornissen bij de hond (Two new cases of hypophyseal disturbances in the dog). Vlaams Diergeneeskundig Tijdschrift 8.

Wolfesberger, B., Fuchs-Baumgartinger, A., Schwendenwein, I., Zeugswetter, F., Shibly, S., 2011. Sudden death in a dog with lymphoplasmacytic hypophysitis. Journal of Comparative Pathology 145, 231–234.

Zublena, F., Tamborini, A., Mooney, C.T., North, S.M., Lobacz, M.A., Andrew, D., Woolhead, V., Covey, H., Schmid, H.A., Church, D.B., Niessen, S.J.M., 2018. Radiotherapy and pasireotide treatment of a growth hormone producing pituitary tumor in a diabetic dog. Canadian Veterinary Journal 59, 1089–1093.