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CUSHING'S SYNDROME

Identifying Prognostic Factors Promotes Novel Treatments

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DACHSHUNDS WITH CUSHING'S SYNDROME

MAY BENEFIT FROM RESEARCH OF TARGETED TREATMENTS

Smitten with the comical, entertaining nature of Dachshunds, Kathleen Frizzell bought a smooth-coated male named "Murphy" in 2006 and a longhaired female named "Reilly" in 2007. Both were bought to be pets. Then, she bought "Millie" (Morgan's I've Got the Time ML), a Miniature Longhair, in 2008 with plans to show her.

"I knew nothing about the breed when I started," says Frizzell, of Milford, Michigan, who breeds Longhaired Dachshunds under the Proud Lake prefix.

She also knew nothing about Cushing's syndrome, one of the most common endocrine diseases in small-breed dogs. A lifelong condition, Cushing's syndrome typically affects middle-aged and older dogs. Not only does it impact a dog's quality of life, untreated

Cushing's syndrome can cause secondary conditions, such as diabetes mellitus, pancreatitis and hypertension.

Just like clockwork, Frizzell's Reilly was diagnosed with Cushing's syndrome in 2016 at 9 years of age, Millie in 2017 at age 9, and Murphy in 2017 at almost 12 years of age. The unrelated Dachshunds were from different breeders.

"I had heard of Cushing's syndrome, but I wasn't really familiar with it," Frizzell says. "I have learned from experience that with the right treatment and care, Dachshunds can live a good life and do well despite having Cushing's syndrome."

An investigator who studies canine Cushing's syndrome, Karin Sanders, DVM, PhD, a postdoctoral researcher at Utrecht University in the Netherlands, says, "Most

Diagnosed with Cushing's syndrome are, from left, "Murphy," "Reilly" and "Millie."



Dachshunds are not diagnosed with Cushing's until at least age 6. The prevalence in Dachshunds is between one in 30 to 40 dogs compared to one in 400 dogs in the general population."

The challenges of diagnosing and treating Cushing's syndrome have intrigued Dr. Sanders. During her doctorate research, she was part of a team that worked on a study led by Dr. Sara Galac that produced the [Utrecht histopathological scoring system](#) used to assess the prognosis for dogs with a cortisol-secreting adrenocortical tumor. Dr. Sanders has used gene expression to identify [markers that predict a dog's prognosis](#) after surgery and guide clinical drug therapy development. Her work with microRNAs has shown them to be effective [biomarkers that provide diagnostic and prognostic presurgical and postsurgical information](#) to shape clinical treatment.

Dr. Sanders' current research looks at providing effective treatments for the pituitary-dependent form of Cushing's syndrome for which treatment options are extremely limited. Using stem cells to grow organoids that mimic tumors, she has created a 3D model that can be used to test targeted treatments. The [AKC Canine Health Foundation](#) and [Morris Animal Foundation](#), with a contribution from the Dachshund Club of America, are supporting this research.

Deneice "Denny" Van Hook, DVM, president of the Dachshund Club of America Health & Welfare Trust, says, "The prevalence of Cushing's syndrome in Dachshunds warrants funding research to discover new treatments. Not a lot has changed over the years in treating this condition. Anything we can do to improve the quality of life and life expectancy of affected dogs is important."



THE EFFECTS OF TOO MUCH CORTISOL

Hypercortisolism is the medical term for Cushing's syndrome. It is named for Henry Cushing, a Johns Hopkins neurosurgeon who first described the disorder in his patients in 1912. Similarities between the disease in people and dogs provide One Health research benefits. Since Cushing's is rare in people, dogs are considered a valuable model to aid understanding.

"Endocrine disorders such as Cushing's syndrome involve glands and hormones," Dr. Sanders explains. "It occurs when the body produces too much cortisol, a hormone made and stored by the adrenal glands that is involved in stress management, body weight regulation, healthy skin, and tissue structure maintenance. Too much cortisol weakens the immune system and can cause a host of clinical signs."

Clinical signs of Cushing's syndrome include:

- Polyuria (frequent urination)
- Polydipsia (excessive thirst)
- Polyphagia (excessive appetite)
- Potbellied appearance
- Muscle weakness
- Hair coat loss
- Panting
- Lethargy

“Reilly spent half her time lapping out of the water bowl and the other half urinating,” recalls Frizzell of the signs that took her to the veterinarian with her first Dachshund diagnosed with Cushing’s syndrome. “Reilly also became aggressive at food time as she would try to steal other dogs’ food.”

“Early diagnosis and treatment are important with Cushing’s syndrome, though it can be challenging to diagnose because clinical signs develop gradually and can mimic other conditions,” says Dr. Sanders. “Relatively low disease prevalence in the general dog population and

a lack of highly accurate diagnostic tests also hinder diagnosis.”

Two types of Cushing’s syndrome are recognized in dogs. The most common type accounting for 80 to 85 percent of cases is pituitary-dependent hypercortisolism (PDH). An adenoma, or noncancerous tumor, develops in the pituitary gland at the base of the brain causing overproduction of adrenocorticotrophic hormone (ACTH) that stimulates the adrenal glands to produce more cortisol than the body needs. The second type attributed to 15 to 20 percent of cases is caused by a cortisol-secreting adrenocortical tumor (ACT) in one or both adrenal glands that produces excess cortisol. An ACT can be benign (an adenoma) or malignant (a carcinoma).

Dogs treated long term with steroid medications for allergies, respiratory illness or autoimmune disease can develop iatrogenic Cushing’s syndrome in which the drugs cause the illness. The steroid medications are glucocorticoids, or cortisol-like drugs, that if given for a long time can mimic the state in which the body itself produces excessive glucocorticoids.

“Diagnosis starts with a veterinary examination and complete blood count analysis. Diagnostic imaging can help detect a tumor in the pituitary gland or adrenal glands,” Dr. Sanders says. “We recommend using the dexamethasone suppression test for confirmation of hypercortisolism, either the low-dose dexamethasone suppression test (LDDST) or the high-dose dexamethasone suppression test (HDDST).”

The HDDST involves determining the urinary corticoid:creatinine ratio (UCCR) in a dog’s morning urine on two consecutive days. Then, a dog is given a high dose of dexamethasone, a synthetic form of cortisol that suppresses cortisol



production by the body, and the UCCR is measured the next day in the morning urine.

The LDDST test involves taking a blood sample and then giving a dog an injection of dexamethasone. Blood samples are taken four hours and eight hours after the injection and compared to the original blood sample to determine whether dexamethasone successfully suppressed cortisol production.

“In a healthy dog you would expect the cortisol value to be completely suppressed after the injection,” says Dr. Sanders. “When the cortisol level stays high but is suppressed for more than 50 percent, compared to the first value, it is practically certain that a dog has pituitary-dependent Cushing’s syndrome. When the cortisol level is not suppressed and stays high, a dog could have pituitary-dependent or adrenal-dependent Cushing’s syndrome.”

“The LDDST test confirmed that Reilly had Cushing’s syndrome after bloodwork was inconclusive,” Frizzell says. “One year later when Murphy showed signs of excessive drinking, urinating and hunger, we started with the LDDST test.”

“Treatment for Cushing’s syndrome ideally involves surgery to remove the tumor providing no metastases are detected,” Dr. Sanders says. “An adrenalectomy is performed to remove the affected adrenal glands in ACT cases. Even with surgery, recurrence rates vary from 12 and 38 percent due to metastases, or tumor regrowth. A hypophysectomy to remove the pituitary gland at the base of the brain in PDH cases is a good treatment option, but because this is a highly specialized surgery, it can only be performed in a small number of clinics worldwide.”

A shortage of veterinary specialty clinics offering the procedures combined with surgical risks and

FACEBOOK SUPPORT GROUPS FOR CANINE CUSHING’S SYNDROME

Dachshunds are among several breeds and even mixed breeds susceptible to Cushing’s syndrome. Two private Facebook groups offer support to owners of affected dogs or those wanting to learn about this common endocrine disorder in small breeds of dog. [Cushing’s Disease in Canine Support Group](#) and [Canine Cushings Support Group](#) provide a forum where members can discuss the disorder, treatment, prognosis, and disease management. Some members share memories of beloved dogs that eventually succumbed to the lifelong disorder.

individual patient cases not being suited for surgery result in dogs more commonly being treated with medications. Trilostane, which is sold as Modrenal® and Vetoryl®, is prescribed for both PDH and ACT Cushing’s syndrome. Although trilostane inhibits the production of cortisol in the adrenal glands, it does not stop tumor growth. Regular monitoring of a dog’s cortisol level via ACTH stimulation testing helps to ensure hormone balance, as too little cortisol can cause other health problems.

“Trilostane was prescribed for all my dogs, starting on a daily dose of 10 milligrams,” Frizzell says. “Reilly was reduced to 5 milligrams at one point because she needed more cortisol. Periodic checkups are required to monitor cortisol levels.”

RESEARCH FOCUSES ON DIAGNOSIS, TREATMENT & PROGNOSIS

“Particularly for pituitary-dependent hypercortisolism, treatment options that target the tumor are limited,” Dr. Sanders says. “As the pituitary tumor continues to grow, it potentially can cause neurological problems. New drug treatments that can inhibit the growth of the pituitary tumor are vitally needed.”

The recently funded studies by Morris Animal Foundation and the AKC Canine Health Foundation are contributing information about



“These miRNAs have the potential to serve as biomarkers in dogs with PDH and ACT Cushing’s syndrome.”

Karin Sanders, DVM, PhD, postdoctoral researcher, Utrecht University, Netherlands

possible novel drug therapies. Both studies involve the development of an *in vitro* 3D miniature model of a canine pituitary tumor made from stem cells to grow organoids that resemble the tumor.

The pituitary tumor-derived organoids provide an effective test model for 10 targeted drug therapies. “We are testing these drugs in different concentrations to evaluate their effectiveness in inhibiting cell proliferation,” she says. “Because we want to make sure that the models that we grow in 3D in the lab are really derived from the tumor cells, we have performed whole-genome sequencing on these pituitary-derived organoids. We are analyzing the results now, and once their origin has been

confirmed, we will proceed with the drug testing.”

The ability to understand a dog’s prognosis and response to treatment for ACT Cushing’s syndrome was the aim of an earlier study led by Dr. Sanders. The findings, published in July 2019 in *Veterinary and Comparative Oncology*, identified several genes that can be used to predict prognosis following an adrenalectomy and that offer insights into effective drug treatments.

The team evaluated ACTs from 14 dogs with a low-risk of recurrence and 26 dogs with a moderate-to-high recurrence risk and compared them with 11 normal adrenals from healthy dogs. Risk ratings were based on the [Utrecht histopathological score](#) for canine Cushing’s disease developed at Utrecht University. The Utrecht score is useful in identifying dogs with high-risk ACT recurrence that might benefit from adjuvant treatment or additional monitoring with a goal of increasing survival.

“Among the 14 candidate genes we studied, seven were differentially expressed between the normal adrenals and the ACTs,” Dr. Sanders says. “These genes are part of the molecular signature of malignancy in canine ACTs. We can use this information to target drug treatments for canine Cushing’s disease.”

The study showed that:

- High-expression levels of steroidogenic factor-1 (*SF-1*), pituitary tumor-transforming gene-1 (*PTTG1*) and topoisomerase 11 alpha (*TOP2A*) genes were significantly associated with poor survival.
- *PTTG1* and *TOP2A* were expressed higher in medium-to-high-risk ACTs compared to low-risk ACTs, which makes them novel treatment targets.

Following this study, Dr. Sanders looked at whether microRNAs (miRNAs) that circulate in the

body could serve as biomarkers to help predict before surgery the risk of tumor recurrence. Tied to gene expression regulation, these noncoding RNAs have been shown to be useful diagnostic and prognostic biomarkers in several diseases including some cancers.

“Our pilot study analyzing blood samples of six healthy dogs, 19 PDH dogs pre- and postsurgically, and 26 ACT dogs presurgically indicated that circulating miRNAs have the potential to be noninvasive biomarkers for dogs with Cushing’s syndrome,” Dr. Sanders says. “We also saw that the miRNAs could contribute to clinical decision-making.”

The hypothesis for the research, published November 2021 in *Frontiers in Veterinary Science*, was that circulating miRNAs could be identified having expression profiles associated with the presence or absence of PDH or ACT Cushing’s syndrome. Dr. Sanders also envisioned that miRNAs would provide insights about tumor size and the likelihood of disease recurrence after a hypophysectomy for PDH type Cushing’s or an adrenalectomy for ACT type Cushing’s.

“We identified several circulating miRNAs that are dysregulated in dogs with Cushing’s syndrome compared to healthy dogs and that have the potential to be noninvasive biomarkers for the disease,” she says.

The miRNA analysis showed:

- miR-122-5p was significantly overexpressed in dogs with PDH Cushing’s syndrome, which was not seen in healthy dogs. This miRNA also was higher in dogs having recurrent disease after hypophysectomy.
- miR-483-30 was overexpressed in dogs with ACT Cushing’s syndrome compared to healthy dogs.

“These miRNAs have the potential to serve as biomarkers in dogs with PDH and ACT Cushing’s syndrome,”

says Dr. Sanders. “They could one day provide a diagnostic and prognostic tool to help veterinarians make treatment decisions.”

LIFETIME MANAGEMENT OF CUSHING’S SYNDROME

Improving survival and quality of life for dogs with Cushing’s syndrome is the aim of Dr. Sanders’ research efforts. In the meantime, prompt diagnosis and treatment combined with owners adhering to medication schedules and veterinary recheck visits offer the best outcome for dogs with Cushing’s syndrome.

Frizzell, whose Dachshunds, Reilly, Millie and Murphy, were diagnosed with Cushing’s syndrome, observes biannual veterinary visits to check cortisol levels and daily trilostane medications. She also monitors her dogs for medication side effects.

Although Millie and Reilly have passed away — Reilly died in December 2021, living almost six years with Cushing’s syndrome — Frizzell continues to care for Murphy, who will celebrate his 16th birthday in 2022. Thus far, Murphy is a five-year survivor of Cushing’s syndrome.

Reflecting on having gone through Cushing’s syndrome with three dogs, Frizzell says, “They have lived very well on the medications. That has made it easier to deal with this disease. Most of all, Dachshunds are loyal and so much fun, and that keeps us all going.” ■

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