Primary hyperaldosteronism (PHA), also known as Conn’s disease or primary aldosteronism, was first described in humans in 1955 and in cats in 1983. Since that time, sporadic case reports have appeared in the literature describing feline PHA, either as the sole pathology, with other endocrinopathies, or in association with neoplastic abnormalities. In humans, PHA was an uncommon diagnosis but is now recognized as the most common cause of endocrine hypertension, the most frequent cause of secondary hypertension. Although debate exists over the best way to diagnose PHA in humans, recent studies suggest that 5% to 13% of patients who have hypertension experience PHA. Similar to early underrecognition in human hypertension, because blood pressure is not always considered part of the minimum database for routine physical assessment of healthy or diseased cats, and because aldosterone is not routinely measured in all cases of feline hypertension, cats may also experience PHA more commonly than is reported.

ALDOSTERONE PHYSIOLOGY

The principal known function of aldosterone is regulation of systemic blood pressure and homeostasis of extracellular fluid volume in response to changes in hemodynamics and electrolytes. Aldosterone acts by increasing secretion of potassium and hydrogen and resorption of sodium and chloride in the distal nephrons of the kidneys. Thus, increased plasma aldosterone concentrations cause increases in sodium concentration and volume of the extracellular fluid.

Aldosterone production in the zona glomerulosa of the adrenal cortex is regulated by the renin–angiotensin system (also called the renin–angiotensin–aldosterone system; RAAS) and extracellular potassium concentrations. The kidneys increase renin secretion in response to a decrease in circulating blood volume or renal blood flow sensed by the juxtaglomerular apparatus. Decreased delivery of sodium and chloride to the macula densa cells in the distal tubules also stimulates renin secretion. Renin cleaves angiotensinogen, produced by the liver, into angiotensin I, which is hydrolyzed to angiotensin II by angiotensin-converting enzyme (ACE). In addition to
being a powerful vasoconstrictor, angiotensin II stimulates aldosterone secretion. Potassium controls aldosterone secretion through a direct effect on the adrenal zona glomerulosa.\textsuperscript{15}

Therefore, when the kidneys experience decreased blood flow, renin, angiotensin II, and aldosterone are increased, resulting in increased sodium retention, increased extracellular fluid volume, and lower extracellular concentrations of potassium (through loss in the urine). Once homeostasis is restored, renin production is reduced and the aldosterone concentration declines. In PHA, excess aldosterone causes systemic hypertension. The increased urinary loss of potassium may result in profound hypokalemia. As potassium shifts extracellularly, hydrogen ions move intracellularly. Metabolic alkalosis may result from the increased urinary loss of hydrogen ions in addition to the intracellular shift.\textsuperscript{14}

**PRIMARY HYPERALDOSTERONISM**

**Clinical Presentation**

Cats diagnosed with PHA are usually geriatric, although one case study includes a cat as young as 5 years.\textsuperscript{5} There do not appear to be sex or breed predilections. Weakness is the most common presenting sign, followed by cervical ventriflexion. The weakness may be acute in onset or more insidious in nature.\textsuperscript{2,3,5–7,9} Hind limb weakness, episodic forelimb stiffness, and dysphagia were also described.\textsuperscript{3} The weakness displayed by cats with PHA is typical of hypokalemic polymyopathy.\textsuperscript{16} Hypokalemia in cats with PHA can also result in lethargy and depression.

Clinical signs related to systemic hypertension may be seen at initial presentation. Of 33 cats described in the literature, 11 presented with blindness caused by retinal detachment and intraocular hemorrhage.\textsuperscript{2–4} Other consequences of systemic hypertension include myocardial hypertrophy and renal damage. Additional presenting signs include polyuria–polydipsia\textsuperscript{3,4} and enuresis\textsuperscript{4} weight loss,\textsuperscript{4,8} diarrhea\textsuperscript{7} and polyphagia.\textsuperscript{3} Some cats with PHA have palpable abdominal masses.\textsuperscript{4,5}

Biochemical abnormalities found in cats with PHA are consistent with the excessive circulating concentrations of aldosterone. Moderate-to-severe degrees of hypokalemia are typically seen, whereas serum sodium concentrations may be normal or mildly increased.\textsuperscript{2–9,17} It is not surprising that the serum sodium concentrations are only mildly increased, if at all, given the increased water resorption that accompanies the aldosterone-driven sodium resorption.\textsuperscript{18} Early in the disease course, serum potassium concentrations may be normal.\textsuperscript{19} Urinary fractional excretion of potassium is greatly increased because of the effects of aldosterone. Serum creatinine kinase concentrations are also usually markedly elevated, secondary to hypokalemic polymyopathy.\textsuperscript{20}

Cats with PHA may have evidence of renal disease, including isosthenuria and increases in serum creatinine and BUN concentrations. Hyperaldosteronism may lead to hyaline arteriolar sclerosis, glomerular sclerosis, tubular atrophy, and interstitial fibrosis, thus causing or worsening chronic kidney disease.\textsuperscript{19} Many hyperaldosteronemic cats that present without azotemia, or only mild azotemia, experience progression of renal disease.\textsuperscript{2,3,19} In cases of adrenal tumors, plasma renin activity is typically low or absent because of negative feedback inhibition from excessive aldosterone. In some cases, renin escapes from suppression because excessive aldosterone results in continued activation of RAAS, progression of renal disease caused by hypertension, and additional damage from excess angiotensin II.\textsuperscript{19,21} Humans with hyperaldosteronism often develop renal cysts and proteinuria. The proteinuria of hyperaldosteronism is of greater magnitude than that seen with primary hypertension.\textsuperscript{12,21–23}
In human medicine, the adverse effects of aldosterone on the cardiovascular system are well established. Aldosterone excess leads to left ventricular hypertrophy and cardiac fibrosis. These changes are more severe than with primary hypertension. Humans who have aldosteronism are at increased risk for cardiac arrhythmias.\textsuperscript{11,22} Many cats diagnosed with hyperaldosteronism had evidence of cardiovascular disease, including cardiac murmurs, radiographic cardiomegaly, or ventricular hypertrophy noted on echocardiogram\textsuperscript{4–8}; the role of the hyperaldosteronism in the generation or progression of cardiac disease in cats is unknown.

Hyperaldosteronism is also implicated in metabolic syndrome, which is characterized by insulin resistance, impaired beta-cell function, excessive proinflammatory proteins, and a prothrombotic tendency.\textsuperscript{22,24} Humans who have metabolic syndrome are at far greater risk for overt diabetes mellitus, heart disease, and stroke. Further work is needed to establish a similar metabolic syndrome in cats.

**Etiology**

In humans, six different subtypes of PHA have been identified. Patients most commonly experience either bilateral idiopathic hyperaldosteronism or an aldosterone-producing adenoma. Less commonly seen causes of PHA in humans include unilateral adrenal hyperplasia and familial hyperaldosteronism (FH), of which two forms, FH type I and FH type II, have been described.\textsuperscript{25}

In cats with PHA, most cases are attributed to either adrenal adenomas or carcinomas. Of 23 cases reported in the literature with histopathologic examination of the affected adrenal glands, 11 developed hyperaldosteronism associated with unilateral carcinoma\textsuperscript{2–4,7,8,17}; 9 were diagnosed with adenomas\textsuperscript{3,5,9}, and 2 of 9 had bilateral disease.\textsuperscript{3} Additionally, in one report 3 cats were diagnosed with bilateral adrenal hyperplasia.\textsuperscript{19}

Feline PHA has also been diagnosed as part of other conditions. One cat had an adrenal carcinoma, which produced excessive amounts of both aldosterone and progesterone.\textsuperscript{8} Another cat had PHA diagnosed as part of multiple endocrine neoplasia I (MEN I). MEN is a well-recognized group of autosomal dominant syndromes in which single human patients develop multiple tumors originating in endocrine organs. The MEN I syndrome usually involves the pancreas, parathyroid glands, and pituitary gland. Adrenocortical neoplasia is found in 13\% to 40\% of humans who have MEN I. The cat described by Reimer and colleagues\textsuperscript{9} was diagnosed with an adrenal adenoma, pancreatic insulin-secreting tumor, and a parathyroid gland adenoma.

**Diagnosis**

When Conn\textsuperscript{1} first described primary hyperaldosteronism in 1955, he discussed three hallmarks: hypertension, hypokalemia, and increased serum aldosterone concentration. In contrast, in secondary hyperaldosteronism, the increase in aldosterone concentration results from a primary increase in renin. Secondary hyperaldosteronism is most often associated with renal disease, cardiovascular disease, and liver failure.\textsuperscript{26}

In veterinary patients, hyperaldosteronism is usually suspected in cats with hypokalemia and hypertension (often refractory) for which another cause cannot be identified. Hypokalemia can result from various disorders, including renal failure, hepatic dysfunction, infection, gastrointestinal disease, cardiac disease, and endocrinopathies such as hyperthyroidism and diabetes mellitus.\textsuperscript{27} A thorough history, physical examination, and minimum database consisting of a complete blood cell count, chemistry profile, and urinalysis will rule out most causes of hypokalemia. Similarly, systemic hypertension can have various causes in the cat, with renal disease and hyperthyroidism among the most common.\textsuperscript{28}
Traditionally, for Conn’s disease in humans, hypokalemia was a necessary finding on screening tests before additional diagnostic testing. This prerequisite resulted in underrecognition of PHA in humans who had hypertension. Currently, hypokalemia is rarely seen in human PHA or found only late in the disease course.\textsuperscript{10,13,25} Similarly, some cats with PHA do not display hypokalemia on initial presentation.

In the 2005 paper by Javadi and colleagues,\textsuperscript{19} 5 of 11 cats with PHA had normal serum potassium concentrations, although 2 did develop hypokalemia. Hypokalemia may represent a much later development in the natural course of the disease. Failure to suspect PHA because of normal potassium results on screening tests may result in underdiagnosis of feline PHA in the hypertensive feline population, and delay in identification and management of individual patients.

Increased aldosterone concentration is the diagnostic hallmark of PHA, both in cats and humans. In humans, aldosterone is measured under controlled conditions. Variables that are controlled include amount of salt in the diet, administration of antihypertensive medications, and patient position at blood draw.\textsuperscript{13} In a group of healthy cats, Javadi and colleagues\textsuperscript{29} described a reference range for plasma aldosterone concentration of 80 to 450 pmol/L (28.8–162.2 pg/mL), which was consistent with human measurements from that same laboratory. Stress and body position did not affect aldosterone concentrations in cats.

Serum aldosterone measurement is widely available at veterinary laboratories. Veterinarians should observe reference ranges provided by the specific laboratory. Patient aldosterone concentrations are interpreted in combination with serum potassium concentrations. Because potassium is a major stimulus for aldosterone secretion, hypokalemia is a potent suppressor of aldosterone secretion in the normal animal. Among some cats with PHA in Javadi’s study, aldosterone concentrations fell within the reference ranges; however, the investigators concluded that the aldosterone concentrations were inappropriately high in light of the concurrent hypokalemia.\textsuperscript{19} Therefore, if an aldosterone concentration is in the high-normal range, but the potassium concentration is low, PHA should still be considered.

Recently, a reference range for the urinary aldosterone:creatinine ratio (UACR) was established for cats. The UACR offers advantages over plasma aldosterone concentrations in that it provides an indication of circulating aldosterone concentrations over time (the time over which the urine is made) without requiring frequent blood sampling or protracted urine collections.\textsuperscript{30} The efficacy of the UACR in cats with spontaneously occurring PHA requires further examination.

In cats with hyperaldosteronemia and hypertension, plasma renin activity should be measured to differentiate primary from secondary hyperaldosteronism. In primary hyperaldosteronism, plasma renin activity is minimal, reflecting the autonomous secretion of aldosterone by the adrenal glands.\textsuperscript{26} In humans, the aldosterone:renin ratio (ARR) is used as the primary screening test for PHA. In both humans and cats, cases of PHA have been reported with normal plasma renin activity, complicating definitive diagnosis.\textsuperscript{19,21}

Hypothetically, in cats with less extremely high aldosterone, such as those with adrenal adenoma rather than adrenal neoplasia, plasma renin activity may remain normal. Cats with severe hyperaldosteronism should have more consistent and measurable suppression of plasma renin activity.\textsuperscript{19} Aging and neutering may also decrease plasma renin activity in healthy cats, thus causing the ARR to be higher.\textsuperscript{29} Unfortunately, measurements of renin activity are not widely available through veterinary laboratories and clinicians often must rely on aldosterone measurement as a solitary test. PHA is often confirmed retrospectively after surgical removal of an adrenal tumor and subsequent dramatic decline in aldosterone concentrations.\textsuperscript{8}
Imaging of the adrenal glands is frequently performed in veterinary patients with PHA. Ultrasound findings in cats include adrenal mass, adrenal calcification, and changes in echogenicity.3–8,17,19 CT and MRI have also been used to improve imaging of the adrenal glands in cats.3,17,19 Of 25 cases with reported advanced imaging, only 2 had normal-appearing adrenal glands on ultrasound or CT.19 However, the finding of an enlarged adrenal gland or adrenal mass does not mean that it is producing excessive aldosterone. Adrenal masses in the cat are often incidental findings known as incidentalomas; other adrenal masses in cats can be attributed to hypercortisolism (cortisol-secreting), pheochromocytomas, and progesterone-secreting tumors.7,8 In contrast to cats, adrenal imaging is performed in human patients only after PHA is diagnosed; imaging is used to help differentiate between unilateral adenomas and bilateral hyperplasia. Most adenomas identified in humans are smaller than 10 to 20 mm and can escape detection with CT and MRI.31

Testing for primary aldosteronism in humans occurs in three phases: case-finding, confirmation, and subtype evaluation. Case-finding testing involves screening of the hypertensive population most likely to experience PHA (unexplained hypokalemia, resistant hypertension, early-onset hypertension, adrenal mass). Screening is typically performed using the ARR. If that test is positive, patients are then confirmed to have PHA using an exclusion test. Exclusion tests suppress aldosterone secretion and are used to rule out false-positives. These tests include those for oral sodium loading, saline infusion, fludrocortisone with salt loading, and captopril.13,25,32 Oral sodium loading was found to be not successful in cats (it did not increase the amount of sodium in the urine in more than half of the cats), nor did oral sodium loading decrease aldosterone secretion. Fludrocortisone administration suppressed urinary aldosterone secretion in three normal cats but not in one cat with confirmed PHA, and therefore may be a useful tool.30 Other aldosterone-suppression testing has not been examined for validity in cats. Subtype evaluation is performed in humans to distinguish between idiopathic bilateral adrenal hyperplasia, which is treated medically, and unilateral adenomas, which are treated surgically, and to differentiate the more uncommon subtypes of PHA. Adrenal vein sampling is considered the gold standard for documenting lateralization of aldosterone secretion, and thus deciding whether surgery should be considered.31

**Treatment and Prognosis**

For cats with unilateral disease, surgical removal of the affected adrenal gland remains preferred treatment. Surgery seems to be curative for both adenomas and carcinomas, with signs of hypokalemia and hypertension resolving without further treatment.3–5,7 Cats surviving the immediate postoperative period often had survival times of many years.3 Cats with carcinomas seem to have a similarly good postsurgical prognosis, as do those with adenomas.3 Invasion of the caudal vena cava from an adrenal tumor, or associated thrombosis is usually considered a contraindication to surgery, but successful outcomes have been reported even with vena cava thrombosis.7 In humans who have unilateral adenomas, surgery is the recommended treatment. Removing the affected adrenal gland has been shown to normalize the RAAS and cure hypokalemia.22,31 Additionally, systemic hypertension is improved in all patients and cured in up to 82%.31

Cats may also do well with medical management, which consists of spironolactone therapy, potassium supplementation, and antihypertensive drugs as needed. Spironolactone is an aldosterone antagonist that binds to the aldosterone receptors in the distal convoluted tubules. Reported survival times for cats treated medically often range from many months to years.3,4 A newer-generation aldosterone antagonist,
Eplerenone, is being examined for use in humans who have PHA. In humans, side effects may arise from spironolactone’s affinity for androgen, estrogen, and progesterone receptors. Eplerenone has a far diminished affinity for these other receptors. Whether this drug would be suitable for use in cats is unknown.

SUMMARY

PHA is being recognized more frequently in cats. Usual hallmarks of the disease include hypokalemia and systemic hypertension. Ultrasound frequently detects an abnormality in the affected adrenal gland. Diagnosis is based on increased plasma or serum aldosterone concentrations, particularly in the face of hypokalemia and low renin activity (when measurement is available). Cats with PHA have good prognoses with surgical excision of tumor-bearing adrenal glands. Medical management can stabilize patients for many months. The reported incidence is unlikely to increase as practitioners become more aware of the condition and diagnose it earlier in the disease course. If veterinarians choose to use humans as an experimental model, PHA should be considered a differential for cats with hypertension of unknown cause or that is refractory to treatment. Using hypokalemia as a definitive criterion in screening for PHA may result in late-stage diagnosis and underrecognition of incidence of PHA in the hypertensive population, and may also explain the discrepancy in the size of the adrenal glands in affected humans (often <10–20 mm) and cats (enlarged enough to be detected by ultrasonography). Adrenal carcinoma seems to be a far more frequent cause of PHA in cats than in humans, but carries a far better prognosis in cats.

REFERENCES