ADRENAL DISEASE AND NEUTERING TECHNIQUES IN SMALL MAMMALS

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Kevin Eatwell discusses approaches to managing procreation system disorders, and looks at the problems associated with adrenal gland disease

REPRODUCTIVE management of small mammals is an important part of the primary care package offered in first opinion practice.

However, in many cases, the promotion of routine neutering is not always offered, despite having marked health benefits to these patients.

Myomorphic rodents

Mice and rats are usually housed in single-sex groups, but pairs or harems are also possible, although neutering is rarely performed.

Mammary neoplasia (usually fibroadenoma) is common in both species, with mice carrying a poor prognosis. However, more usually, rats present to the clinic for removal of mammary masses. Growth often recurs, as the mammary tissue is extensive. Ovariectomised rats have a significantly lower incidence. Mammary mass removal can be performed simply via a bilateral flank incision to remove both ovaries when the rats are aged two to three months (they reach sexual maturity at eight weeks). It is a simple procedure when performed in lean, young rats with minimal underlying disease.

Males are also usually left entire, but testicular neoplasia can be seen, and this may promote neutering at a later stage. In mixed sex groups, typically the males are neutered to prevent reproduction. The inguinal canals must be closed to prevent herniation.

Gerbils can be kept in bonded pairs and, on occasion, neutering of the males will be requested. Older females (more than two years of age) are prone to cystic ovarian disease, and early detection and removal is advised.

Neutering Syrian hamsters is usually reserved for those cases where there is obvious clinical pathology, as they are kept singly. Findings can include uterine neoplasia or pyometra in females, and it is important to differentiate normal oestrus (this occurs every four days), when a white stringy mucous will be passed, from genuine uterine infection.

On cytology, oestrus secretions have bacteria and epithelial cells present, and abnormal discharges may contain red cells and neutrophils. Uterine and ovarian neoplasia have also been reported.

Males often present at sexual maturity when their flank scent glands start producing secretions and there is fur loss over the gland. Cystic ovarian disease and uterine tumours have also been reported in other hamster species.

Hystricomorphic rodents

Reproductive disease is common in female guinea pigs – cystic ovarian disease is commonly seen in more than 76 per cent of females and can present at an early age.

Cysts can become functional, leading to hormone production. Clinical signs include fur loss, excessive oestrus behaviour and abdominal masses. In other guinea pigs, the cysts can get so large (and presumably cause discomfort) that anorexia is a presenting complaint. Uterine pathology is often associated with this, and leiomyomas and endometritis are commonly identified. Ovarian cyst treatment includes surgical removal, but medical treatment with human chorionic gonadotropin (hCG; 100 international units once a week for three weeks by injection) can be used alongside percutaneous drainage. Treatment with deslorelin implants has also been attempted by this author, but with limited success as cyst size has not altered.

Guinea pigs have a long uterus, which makes removal technically challenging. As a result, routine ovariohysterectomy of guinea pigs is not commonly performed. However, ovariectomy is a simple procedure when performed in young females aged three to four months (once sexually mature) and would be preferable to cystic ovary removal in later life. As owners become increasingly aware that guinea pigs require guinea pig companionship, requests for neutering may increase. In addition, the pubic symphysis fuses at a young age in guinea pigs and, if breeding is required, the females must be bred before seven months of age or dystocia is likely.

If mixed-sexed groups are being kept, neutering the males when they are four months old is advised. Males can be kept together, but they can fight and this can commonly lead to requests for neutering in an attempt to reduce the severity. If this proves unsuccessful, the males could subsequently be housed (separately) with a female, but castration must be closed to avoid inguinal herniation.

Chinchillas are often kept in pairs and male neutering is commonly performed. It is important to ensure the inguinal canals are closed during surgery, otherwise intestinal herniation is likely.

• **Rabbits**

Rabbits are best housed in pairs or harems. Males can fight and neutering can help to reduce aggression. Housing a neutered male with a female is another option. Entire females can also be housed together, and they reach sexual maturity at around four months. They are induced ovulators, but can ovulate in response to petting or mounting from other rabbits, which can lead to a pseudopregnancy.

Pseudopregnant females will exhibit nesting behaviour, such as pulling fur from their abdomens and carrying nesting material around. Pseudopregnancy lasts for 15 to 17 days, and they will also have increased scent marking and territorial behaviour. This can result in increased aggression – not only to other rabbits, but also their owners. Reproductive disease is common in older females – the most common is uterine adenocarcinoma, with 80 per cent of females over five years having the condition. Metastasis to lung, bone, brain and liver, and seeding within the peritoneal cavity are all commonly seen. Other uterine pathologies seen include polyps, endometrial venous aneurysms, pyometras and hydrometras. In older rabbits, mammary gland pathology is often seen associated with uterine disease.

Routine neutering of female rabbits is advised – they have a bicornuate uterus with two cervices in the caudal abdomen. Ovariohysterectomies are commonly performed in practice, but bilateral flank ovariectomy (or laparoscopic ovariectomy) can be performed in young animals. However, no long-term data exists on the development of uterine pathology in these cases.

• **Ferrets**

Female ferrets are seasonally monoestrous, and require the physical act of mating to bring them out of oestrus. The breeding season is usually between March and September. If not mated, they can remain in season for up to six months.

Prolonged exposure to high oestrogen levels results in bone marrow suppression and pancytopenia. Clinical signs include swelling of the vulva (as the female will be in oestrus), vulvar discharge, pale mucous membranes, systolic murmurs, weakness, collapse, alopecia, spontaneous haemorrhage, ecchymoses and petechiation of the skin and mucous membranes,

posterior paresis (due to haemorrhagic myelomalacia) and systemic infections secondary to leukopaenia. Death can occur if it is untreated.

Other causes of hyperoestrogenism include, rarely, an ovarian remnant following ovariohysterectomy, or more commonly, adrenal neoplasia. Pseudopregnancy following a sterile mating has been recorded in ferrets – the diagnosis is based on history, clinical signs and haematology. Treatment with supportive care and a cessation of oestrus is indicated; the former should take the form of administering intravenous fluids, syringe feeding, iron and vitamin B supplementation and prophylactic antibiotics. A blood transfusion is indicated if the packed-cell volume (PCV) is less than 15 per cent – normal PCV values in ferrets range from 46 per cent to 61 per cent. Blood groups have not been demonstrated in ferrets and, therefore, multiple transfusions from the same donor or a variety of donors without cross-matching may be carried out without reactions occurring.

Typically, a healthy larger hob can be used. Jills can be transfused via intravenous or intraosseous routes. With a PCV between 15 to 25 per cent, the prognosis is still poor since this value often continues to decrease over time, but if greater than 25 per cent, cessation of oestrus may be curative.

It is important to bring the jill out of heat. This can be performed by injections of hCG at 100 international units by intramuscular injection. The injection is repeated after seven days if signs of oestrus are still apparent; 50mg proligestone (the ’jill jab”) or gonadotropin-releasing hormone (GnRH) agonists (such as deslorelin; 4.7mg implants are commercially available) can also be used, but have a delay in onset. This condition is easily prevented in female ferrets by:

• mating with a vasectomised male (or an entire male);

• injection of proligestone;

• deslorelin implantation;

• hCG injections;

• melatonin implants;

• ovariohysterectomy; or

• physical stimulation.

Data shows that neutering at any age predisposes to adrenal gland disease and this has brought the ethics of ferret gonadectomy into question. Placement of deslorelin implants has been shown to sterilise male and female ferrets. Typically, females are brought into season for the first two weeks

and then taken out of season. The males are considered sterile after one month, and the current recommendation is to implant a deslorelin implant every two years.

The jill jab is still commonly used, and takes seven to 14 days to work. Many keepers present female ferrets annually for this, and it is anticipated that 20 per cent may require a second injection by the end of the season – in extreme cases, a third may be needed.

Vasectomised hobs are often used as the most economical solution when multiple jills are owned, as they maintain libido for a number of years (two or three) and service the females, bringing them out of season.

Adrenal disease

• Myomorphic rodents

Adrenal adenomas are common in Syrian hamsters, particularly males. These lead to the clinical presentation of Cushing's disease – clinical signs include flank and thigh alopecia, hyperpigmentation, thin skin, hepatomegaly, polydipsia, polyuria, polyphagia and behavioural changes. There are many differentials to consider, as in many cases the history can be limited.

Differentials for the skin disease include ectoparasites, dermatophytosis, hypothyroidism and epitheliotrophic lymphoma – the diagnosis rests on high plasma cortisol levels and ruling out other diseases. Treatment is usually unrewarding, but treatment with metyrapone has been reported. Pituitary disease also occurs with hamsters, and adrenal gland adenomas and adenocarcinomas have also been reported in gerbils.

• Hystricomorphic rodents

Cushing's disease has been reported in guinea pigs – clinical signs noted included nonpruritic bilateral alopecia, weight loss, polydipsia, anorexia and bilateral exophthalmos. The diagnosis of Cushing's disease was based on adrenal ultrasound, which demonstrated enlarged glands. Salivary cortisol levels and an adrenocorticotropic hormone response test were also performed, and treatment with trilostane orally was successful.

• Rabbits

Adrenal gland disease has been anecdotally noted in rabbits – cases seen have been neutered males that have returned to sexual activity. Abdominal ultrasound has been used to confirm enlarged adrenal glands.

• Ferrets

Hyperadrenocorticism, also referred to as adrenocortical disease, or adrenal gland disease, is considered to be one of the most common diseases in ferrets. Both male and female ferrets are affected equally, although typically females are presented more frequently.

Hyperadrenocorticism in ferrets is different from Cushing's disease in dogs and cats. In the latter species, elevated plasma cortisol concentrations are characteristic, while in ferrets, plasma androstenedione, 17-hydroxyprogesterone and oestradiol concentrations are increased. In approximately 85 per cent of ferrets with hyperadrenocorticism, one adrenal gland is enlarged without atrophy of the contralateral adrenal gland, while in the remaining 15 per cent of cases there is bilateral enlargement.

After unilateral adrenalectomy in the case of unilateral enlargement, the disease may recur due to enlargement of the contralateral adrenal gland. Histological changes of the adrenals range from (nodular) hyperplasia to adenoma and adenocarcinoma. The histological diagnosis, however, does not provide any prognostic information. No functional pituitary tumours have been found in ferrets with hyperadrenocorticism.

The most prominent sign of hyperadrenocorticism in ferrets is symmetrical alopecia, and pruritis can also be seen. The skin itself is usually not affected, although some excoriations may be seen. The alopecia usually begins in spring, which coincides with the start of the breeding season, and may disappear without treatment. The next year, the alopecia usually returns, but may not resolve spontaneously at the end of the breeding season.

Reproductive signs can also be seen, with vulvar swelling in neutered jills and a recurrence of sexual behaviour after neutering in hobs. Other concurrent signs include dysuria and urinary obstruction in males, due to peri-prostatic or peri-urethral cysts, and prostatic enlargement. Mammary gland enlargement in jills is occasionally also seen.

When entire, the release of oestrogen and testosterone causes a negative feedback loop on the pituitary gland, and this then switches off production of luteinising hormone (LH) and follicle-stimulating hormone (FSH). Therefore, this release is pulsatile, but when neutered there is no negative feedback loop and the release of LH and FSH continues. This unopposed secretion leads to the production of hormones from the adrenal gland, and adrenocortical hyperplasia and subsequent neoplasia occurs. Eighty-five per cent have one gland affected, and the remaining 15 per cent have both.

Strong support for this hypothesis may be found in the fact that the depot GnRH agonists, leuprolide acetate and deslorelin, can be used successfully to treat ferrets with hyperadrenocorticism. Progression to disease can be seen approximately 3.5 years after neutering (irrespective of their age at neutering).

Clinical signs are the most important tool in diagnosing hyperadrenocorticism in ferrets. A serum

adrenal panel can be used, which consists of androstenedione, oestradiol, and 17-hydroxyprogesterone (0.5ml of heparin blood is required). Elevation of one or more of these hormones is considered diagnostic for active gonadal tissue. This test does not differentiate between hyperadrenocorticism, ovarian remnants or an entire animal, and cortisol is of no use in the diagnosis.

An abdominal ultrasonographic examination is one of the most useful tools in the diagnosis of hyperadrenocorticism, enabling determination if one or both adrenal glands are affected, or if an ovarian remnant is present. To be able to distinguish an adrenal gland from an abdominal lymph node, specific landmarks need to be used.

The left adrenal gland is located ventrolateral to the aorta, at the level of and/or immediately caudal to the origin of the cranial mesenteric artery. The right adrenal gland is located more cranial than the left, and is attached to the dorsolateral surface of the caudal vena cava, at the level of and/or immediately cranial to the origin of the cranial mesenteric artery, and lies adjacent to the caudomedial aspect of the caudate process of the caudate liver lobe.

Locating these structures during an ultrasonographic examination enables visualisation of the adrenal glands in nearly 100 per cent of cases. The adrenal glands of ferrets with hyperadrenocorticism have a significantly increased thickness (greater than 3.9mm), a rounded appearance, a heterogeneous structure, an increased echogenicity and, sometimes, may contain signs of mineralisation. The most important differential diagnoses include a non-ovariectomised female or presence of active remnant ovaries, which can be easily identified on ultrasound.

The treatment of choice is surgery – the left adrenal gland can be fairly easily removed (this lies in a large fat pad cranial to the kidney). The right gland is in a fat pad, and lies more cranially and under the caudal lobe of the liver.

Resection of the right adrenal gland is more difficult due to its dorsolateral attachment to the caudal vena cava. During resection, either a part of the adrenal gland needs to be left attached to the vena cava, or part of the wall of the vein has to be removed. Some veterinarians have ligated the caudal vena cava, but there is a risk of hypertension distal to ligation, which may lead to acute kidney failure. The right gland can, in aggressive cases, invade the vessel.

Haemostatic clips are usually required to facilitate removal of the glands. The phrenicoabdominal veins course over the glands and must be ligated to obtain access. Ligating clips are required to carefully remove the gland, and can be placed on the vessel wall to partially occlude this vessel. Sterile cotton buds can be used to ensure haemostasis is successful. Cryosurgery has been used to ablate glands as an alternative. Radiosurgical instruments should not be used, as thermal damage to the vena cava is possible.

In case of bilateral adrenocortical tumours, different surgical protocols have been proposed. Some

people advise removing the largest adrenal gland and part of the other affected gland. Others advise removing both adrenal glands. When removing both glands, there is a chance of inducing an Addisonian crisis.

Partial removal is another option to reduce the risk of hypoadrenocorticism. That said, many patients develop insulinomas and require steroidal therapy anyway.

Different medical treatments have been proposed for hyperadrenocorticism in ferrets. Aromatase inhibitors, such as anastrozole, are available in the UK, and act by inhibiting oestrogen production. Leuprorelin is a depot GnRH agonist and has regularly been used to inhibit hormone production. Deslorelin implants are now commercially available and are the current treatment of choice. Depot GnRH agonists work because hormones produced by the hypothalamus and pituitary gland are released in a pulsatile fashion. For the release of gonadotrophins, a pulsatile release of GnRH is necessary. By giving an implant with a GnRH-agonist, this pulsatile release is blocked, resulting in a single increased release of gonadotrophins followed by baseline concentrations. As a result, there is cessation of hormone secretion by the adrenal glands and disappearance of clinical signs.

However, the tumour does not decrease in size and may continue to grow, despite the masking of clinical signs.

Complications

In males, one of the potential complications of adrenal gland disease is prostatic cysts. These can get very large and can lead to stranguria and dysuria.

Medical treatment of adrenal gland disease may not lead to resolution and surgical therapy is indicated. These cases can be identified on ultrasound – the fluid contents can be green and viscous with particulate matter. Small cysts can be aspirated at surgery and this may be all that is required.

Ablation of the cysts followed by omentalisation (where the omentum is sutured into an incision into the cyst to allow drainage) may have to be performed in severe cases. Secondary infection and abscessation is also seen. Marsupialisation of the cyst to the bladder has also been performed to facilitate longterm drainage.