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Genetic Tests for Cats: What the Practitioner Needs to Know

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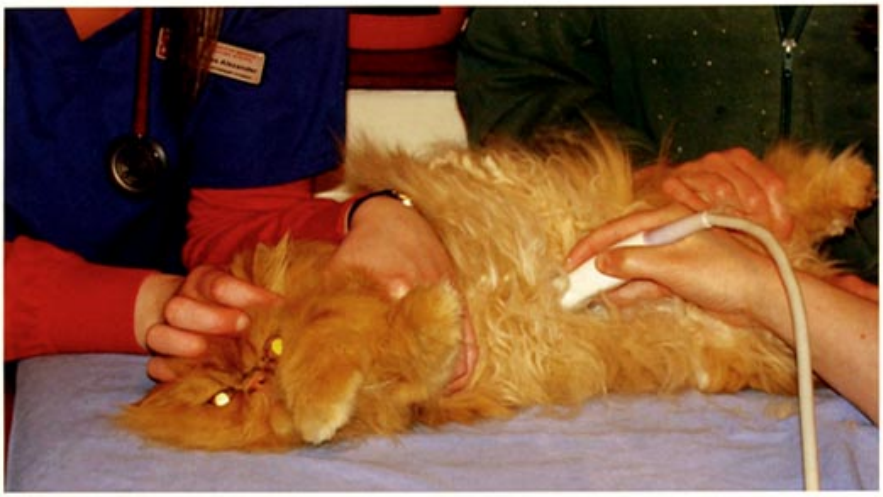

Figure 1: A Persian cat having an ultrasound scan to look for renal cysts seen in polycystic kidney disease (PKD).

Introduction to Genetic Tests for Cats

There have been major advances in the ability to identify genetic mutations in recent years and this has led to ready availability of a number of genetic tests for cats. This article will provide some background information on genetic tests as well as guiding the practitioner on how specific tests can be used in practice.

The first specific gene mutations for feline inherited disease were identified in the first half of the 1990s for a form of muscular dystrophy and some forms of storage diseases, which were also well-known inborn errors of metabolism in humans. At this time the use of a candidate gene approach was the most realistic technique for identifying gene mutations in cats. This technique was based on looking for comparable mutations that had been identified as the underlying cause of similar genetic diseases in other species, often man; as human and cat gene sequences are over 70% identical. Some preliminary characterisation of feline chromosomes had been established at this stage using techniques such as chromosome banding and painting. Chromosome studies facilitated the location of particular genes in the cat genome. Linkage maps subsequently became available, which are based on microsatellite markers and large families of cats. This work was facilitated by genomic studies of hybrid cats, such as the Bengal, by differentiating genes derived from domestic cats and the Asian Leopard. Family-based linkage analyses have enabled the mapping of some genetic defects of cats such as spinal atrophy.

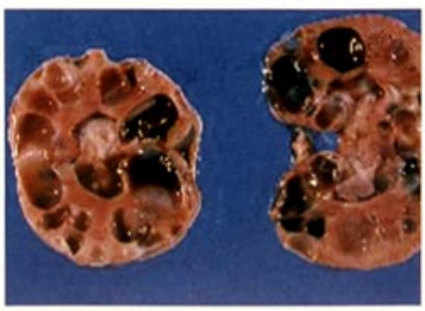

Figure 2: Kidneys from a Persian cat affected with PKD.

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More recently a rudimentary genomic sequence has been published and was developed from in an inbred Abyssinian cat called Cinnamon. Cinnamon came from a colony of cats that had been inbred as part of a study to identify the genetic basis of a form of progressive retinal atrophy (PRA) seen in Abyssinians. The genomic sequence provides a much more powerful tool for identifying genetic mutations in cats and has led to the availability of a number of new genetic tests for cats in recent years. The genetic sequence allows the identification of a large number (several hundred thousand) of single nucleotide polymorphisms (SNPs), that facilitate the identification of genetic traits. These resources are likely to lead to a further massive explosion in our knowledge of genetic diseases and availability of practical tools to deal with these in the coming years as outlined later in the article.

Are these tests of any relevance to our non-pedigree cats?

Inherited genetic diseases are inevitably more commonly encountered in pedigree animals due to selective breeding leading to some degree of inbreeding. However, a number of genetic diseases have been first identified in non-pedigree cats; such as some of the storage diseases. Genetic mutations are often more easily identified in a group of closely related cats of known ancestry, as in pedigree breeds.

and some genetic tests have been developed using pedigree cats. However, these tests may also prove of value in diagnosing some genetic mutations of non-pedigree cats.

Some of the more common and important genetic mutations that have been identified in recent years are based on autosomal dominant genes e.g. polycystic kidney disease (PKD) seen primarily in Persian cats *(figure 1 and 2)* and related breeds and familial hypertrophic cardiomyopathy (HCM), now characterised in Maine Coon *(figure 3 and 4)* and Ragdoll cats. These mutations appear to be prevalent in the high-risk breeds, present in up to 30-40% of individuals.

Figure 3: A Maine Coon cat, this breed, along with Ragdoll cats, is affected by hypertrophic cardiomyopathy (HCM) and a genetic test for the causal mutation is now available

Since these genetic disorders are based on autosomal dominant mutations, affected cats can arise from the first crossing of a pedigree cat carrying the gene with a non-pedigree. As a substantial number of mixed-breed pet cats come from such crossings the genetic tests can be of value in helping the practitioner to diagnose these genetic defects in non-pedigree as well as pedigree cats.

Whilst these genetic tests may be of value in diagnosing genetic diseases, the main indication for their use is to the breeder in avoiding genetic diseases by screening potential breeding cats which may be carrying the undesirable mutation.

What genetic tests are available for cats?

There is now a substantial list of genetic tests available. These tests fall into two main groups – tests for genetic diseases *(table 1)* and tests for genes which confer specific phenotypes i.e. coat colour *(table 2)*.

Table 1 shows the tests for genetic diseases currently available. Once a genetic mutation has been published, other laboratories are able to use this information to develop tests (although there may be differences in the methods used to detect the mutation) subject to any patent considerations which may vary from one country to another. Thus tests may soon become available through a range of laboratories. The leading laboratory for cat genetic tests is the Veterinary Genetics Laboratory (VGL) at the University of California, Davis (UC Davis) (http://www.vgl.ucdavis.edu/). The Diagnostic Laboratories at Langford Veterinary Services, Langford (http://www.langfordvets.co.uk/diagnostic_laboratories.htm) have a long tradition of specialising in diagnostic tests for cats and has been working closely with other researchers working in this area. These collaborations have led to the availability of a number of genetic tests for cats via the Diagnostic Laboratories *(see table 1)* and we are the leading laboratory in this field in the UK.

What samples are required for genetic tests?

Originally most genetic tests required a blood sample, however, as techniques for extraction of DNA from samples have improved and the tests have become more sensitive, buccal swabs are acceptable for most tests. The procedure for collecting samples is simple (see http://www.langfordvets.co.uk/lab_pkdsampling.htm for a video of the technique). Standard swabs including cotton buds/Q tips are generally suitable. Swabs should be packaged to ensure that no cross contamination can occur e.g. a plastic zip-lock bag or clean, unused envelope or by replacing the swab in the plastic sheath.

What other tests are available?

The UC Davis VGL offers a wide range of tests for different coat colour gene mutations and other related tests as shown in table 2. These are often used by breeders to identify if their cats are carrying certain coat colours to decide suitable matings. Another genetic test which breeders make use of is a test for blood group mutations. Practitioners will be familiar with the relevance of blood groups in cats and their importance in transfusions. It is recommended

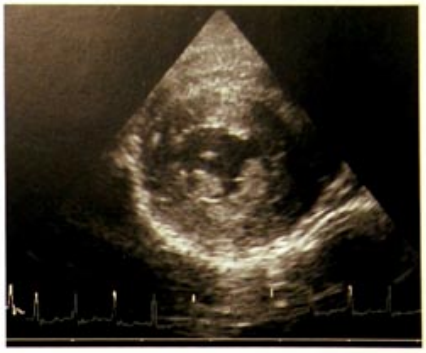


Figure 4: An echocardiographic image of the left ventricle of a Maine Coon cat with HCM illustrating the ventricular wall thickening seen in this disease

that both donor and recipient cats are blood typed prior to transfusion to avoid incompatibility which can lead to potentially fatal transfusion reactions. Testing cards are available to enable the blood group to be determined easily in practice, or samples can be submitted to a diagnostic laboratory. Awareness of blood groups is also important to avoid neonatal isoerythrolysis (NI). NI can occur when a group B queen produces group A kittens (if mated to a group A tom) resulting in a haemolytic crisis in the kittens that absorb anti-A antibodies from their mother's colostrum, often leading to death in the first few days of life. This is a particular concern to pedigree breeders who have breeds with a relatively high

Genetic Disease	Affected Breeds
Polycystic kidney disease*	Persians, British Shorthair, Exotic Shorthair, Himalayan, Scottish fold
Hypertrophic cardiomyopathy*	Maine Coon and Ragdoll
Pyruvate kinase deficiency*	Abyssinian, Somali
Storage diseases	
Gangliosidosis 1	Korat, Siamese
Gangliosidosis 2	Burmese
Gangliosidosis 2	Korat
Glycogen storage disease IV	Norwegian Forest
Progresive retinal atrophy	Abyssinian, Somali, Ocicat
Spinal muscular atrophy	Maine Coon

Table 1: Genetic disease mutation tests available for cats *= available at The Diagnostic Laboratories, Langford Veterinary Services.

Characteristic	Breeds Affected
Agouti	All breeds
Amber	Norwegian Forest
Brown	All breeds
Dilution	All breeds
Colour - Burmese colour pattern, Siamese colour pattern, Full Albino	All breeds
Long fur	All breeds
AB blood group	As indicated

Table 2: Genetic tests available for coat colour and other characteristics.

proportion of group B individuals, notably British Shorthair, Birmans and Rexs. Breeders can use blood grouping of breeding cats to avoid matings that could potentially lead to isoerythrolysis or to take preventative action if necessary. Use of the genetic test has the advantage of detecting not only group B cats but also cats that are carrying the B gene. The predominant blood group A, and the relatively rare AB are dominant to B so mating two type A cats that carry the B gene could result in type B kittens. The genetic test will not differentiate between group A and AB individuals.

Can owners submit samples?

This question has posed a dilemma for our diagnostic laboratory. In the past we have accepted only samples from veterinary surgeons. However, now that most tests can be performed on buccal swabs rather than blood samples it is feasible for owners to submit samples directly. The majority of breeders were choosing this option, sending samples to laboratories overseas rather than collecting a blood sample. To become more competitive we have decided to accept samples directly from owners. However, we stress the value of local veterinary input in counselling for interpretation of results. Tests for which the owners wish to include their cats in an official registry, such as the Feline Advisory Bureau (FAB) PKD and HCM registers (http://www.fabcats.org/breeders/registers.php), require samples to be submitted by a veterinary practice following verification of the cat sampled through a microchip.

An additional factor in accepting samples submitted directly from the owners is that this facilitates development of new genetic tests, which usually necessitates collection of samples from large numbers of cats both affected and unaffected. We frequently work with specific breed clubs, taking samples at shows, to facilitate this work.

How should results be interpreted and owners counselled?

Test interpretation and counselling will clearly depend on a number of factors including the importance of the mutation, prevalence, mode of inheritance and the relationship between phenotype and genotype (i.e. how likely is the genetic mutation to result in clinically significant disease). The practitioner has a crucial role in counselling clients on how to act on results.

For some defects the relationship between genotype and the likelihood of disease is not straightforward. This is particularly true of some of the important dominant genetic mutations such as PKD and HCM. Whilst availability of genetic tests has made an important contribution to advancing our knowledge of inherited disorders, some tests have raised important unanswered questions. For example considering HCM; the inheritance had been recognised as following an autosomal dominant pattern prior to development of a genetic test and it had been presumed that homozygotes were lethal and did not exist. However, since the development of genetic tests homozygotes have been identified, although at a lower frequency than might be anticipated compared to the heterozygotes (which are around 30%).

One explanation for this lower prevalence is that clinical disease may occur at an earlier age and more severely in homozygotes leading to early deaths. However, a significant number of old (>10 years) homozygous individuals have been identified that do not show any evidence of cardiomyopathy. It is also clear that clinical disease will not develop in all heterozygotes; although about 30% of the Maine Coon and Ragdoll populations appear to be heterozygotes the prevalence of clinical disease in these breeds is plainly considerably lower. The same applies to PKD, another autosomal dominant defect that has been shown to have a very high prevalence in Persians and closely related breeds. There is clear evidence from studies based on scanning Persians that once a cat carrying the gene mutation has reached 6-12 months of age it will invariably develop renal cysts. Yet not all, and probably a relatively small proportion of these cats will subsequently develop renal failure.

The most likely explanation for this finding is incomplete or variable expression of these genes, or there may be other genes which influence the likelihood of disease developing.

Can genetic tests help in the diagnosis of disease?

In most clinical cases diagnosis of genetic diseases is based on clinical investigations supported by appropriate diagnostic aids such as laboratory testing and imaging. However, genetic testing can play a role in diagnosis of some inherited diseases, particularly if clinical signs are variable and inconsistently present, such as pyruvate kinase deficiency in Abyssinians *(figure 5)* and Somali cats, which causes waxing and waning anaemia.

Figure 5: An Abyssinian cat, this breed, along with Somali cats, is affected by Pyruvate kinase deficiency which can result in anaemia; and for which mutation a genetic test is now available

Genetic tests can also be used to predict if an individual cat is likely to develop a specific genetic disease. However, as mentioned above, in some cases the genotype will not always predict disease and cats may remain unaffected throughout their lives. A Ragdoll or Maine Coon cat carrying the mutant gene for HCM may not develop cardiomyopathy, although the presence of the gene significantly increases the risk. Conversely a negative test does not guarantee a cat will not succumb to cardiomyopathy due to other, unidentified, gene mutations or secondary to another disease such as hyperthyroidism.

How should genetic tests be used as an aid to preventing inherited diseases?

Genetic tests now provide a realistic tool for breeding programs to eliminate specific inherited disorders. It is possible for owners to test all breeding cats for mutations for which a test is available and eliminate the mutation within a generation. However, there can be disadvantages with this approach. In the case of a dominant gene mutation, such as PKD and HCM, the prevalence within affected breeds is high and if those cats are eliminated from the breeding pool it may significantly restrict the genetic diversity within the breed with unpredictable consequences such as the emergence of a different genetic disease. A more pragmatic approach is to continue to use a restricted number of carrier individuals, which are of high breeding value for other reasons. These should be bred to cats negative for the mutation and their offspring should be tested, half of which would be expected to be negative and could be considered for future breeding.

Control of recessive gene mutations is generally more straightforward. The prevalence of recessive genes is usually relatively low in the population and therefore selecting against these genes will have a lesser effect on the gene pool. It is also possible to continue to use carrier cats without producing affected offspring by ensuring that they are mated only with individuals that have tested negative.

Future developments in genetic testing

There is likely to be further refinement of the genetic map and genomic sequence for cats which will facilitate further development of new genetic tests. There are also important technological developments that will contribute to further advances. A 'SNP chip' for cats is being developed supported by the Morris Animal Foundation which received a substantial donation from Hill's Pet Nutrition for this purpose. This 'chip' will greatly facilitate large-scale studies and will make it possible to look for genetic markers for more complex, multiple gene associated disorders. For example, studies are being initiated to search for genetic markers for diabetes mellitus in cats. Another potential application will be to investigate possible genetic susceptibility to feline infectious peritonitis (FIP). This may enable breeders to select cats with natural resistance in the future.

Genetic testing is now playing an increasingly important role in identifying people who are at particular risk of certain diseases for whom, routine screening is a priority; for example susceptibility to breast cancer. Similar approaches may make it possible to identify cats at increased risk of certain diseases and allow early interventions, for example avoiding obesity in cats at risk of diabetes mellitus.

INTRODUCTION

The cat with seizures is typically presented in different scenarios. The first is when a patient arrives at the surgery with status epilepticus or cluster seizures. The second situation is that of a more chronic presentation, when the owner reports episodic events but the seizuring event is not seen in the surgery. Both situations present different challenges, the patient in status epilepticus requires prompt emergency treatment to terminate seizure activity and prevent long-lasting cerebral damage. The second setting requires exclusion of other causes of paroxysmal events, for example syncope, which may be challenging particularly in cases of partial seizures. The approach to investigation and management of both types of patients is however similar and will be covered in this article.

TYPES OF SEIZURES

Seizures are described by their behaviour (generalised or partial activity), pattern (e.g. isolated, cluster, status epilepticus) and by their aetiology (reactive, idiopathic, symptomatic or cryptogenic).

SEIZURE BEHAVIOUR OR ACTIVITY

Generalised seizures, previously referred to as grand mal, involve both cerebral hemispheres. This form of seizure typically manifests as tonic-clonic activity, with loss of consciousness and autonomic activity including involuntary urination, defaecation and hypersalivation. Other types of generalised seizures are myoclonic, clonic, atonic and absence forms (the latter is well recognised in humans, although not confirmed in cats).

Focal (or partial) seizure activity, previously termed petit mal, arises from a single focus in one of the cerebral hemispheres and may spread to involve the whole cerebrum. Focal seizures may manifest with motor signs, commonly facial muscle twitching or with complex behavioural patterns with impaired consciousness and/or bizarre behavioural activity *(Podell, 2008)*. Examples of focal seizure activities include unilateral limb tremors, ptyalism, excessive vocalisation, manic behaviour including random running and biting at the flanks. Cats develop partial seizures more commonly than canine patients. With recurrent partial seizure activity this form of seizure may progress to more typical generalised activity, as further seizure foci develop within the brain. This process is known as 'kindling'. Partial seizure activity is typically more subtle and can be challenging to recognise.

Permethrin toxicity

Sadly permethrin toxicity remains a common cause of seizures in cats, with the VPIS predicting around 300 cases per year with up to 10% resulting in a fatality *(Sutton et al, JMFS 2007)*. Intoxication most commonly occurs due to inadvertent topical application of spot-on products designed for dogs, or due to direct contact with a dog that has been recently treated. The most common sign asociated with permethrin toxicity is seizures, followed by tremors, hypersalivation and ataxia. Treatment involves dermal decontamination (clipping coat and washing with a mild detergent, application of an Elizabethan collar), and management of seizures as below. **Methocarbamol**, a centrally acting muscle relaxant has been advocated for control of of muscle tremors (55-220 mg/kg PO, to a maximum dose of 330 mg/kg/day *(Volmer et al, 1998a)*.

SEIZURE PATTERN

Characterising the pattern or frequency of seizures is required to assess for any progression of disease, to decide whether anti-epileptic therapy should be instituted and to establish a baseline to assess the response to the therapy.

- Isolated: single seizure
- Cluster: more than 2 seizures in a 24 hour period
- Status epilepticus: continuous seizure activity for more than 5 minutes or 2 or more seizures without recovery in between
- Epilepsy: recurrent seizures

EXTRA-CRANIAL CAUSES OF SEIZURES

These occur when the brain reacts to a systemic insult. Essentially the brain structure is normal. This category can be divided into endogenous and exogenous causes.

Endogenous disease includes metabolic abnormalities and nutritional disorders. Metabolic causes to consider include hypoglycaemia (e.g. insulin overdose, sepsis, hepatic failure), hypocalcaemia (e.g. post bilateral thyroidectomy with iatrogenic parathyroid gland damage), hypo or hypernatraemia, erythrocytosis, hepatic encephalopathy, uraemia and hypertension (e.g. secondary to hyperthyroidism).

Fortunately nutritional causes of seizures are rare, however an unbalanced diet may lead to thiamine and taurine deficiencies, which may manifest with neurological signs.

Exogenous causes of seizures include intoxication by poisons and adverse effects of therapeutics (e.g. metronidazole). Common toxins include ethylene glycol (anti-freeze), permethrin (see box above), organophosphates, metaldehyde and lead. Recent news reports have sadly described clusters of cases of ethylene glycol toxicity in the South West UK. It is unknown whether these are malicious, or due to the increased popularity of water features treated with anti-freeze, this should no longer be considered as a 'seasonal' differential.

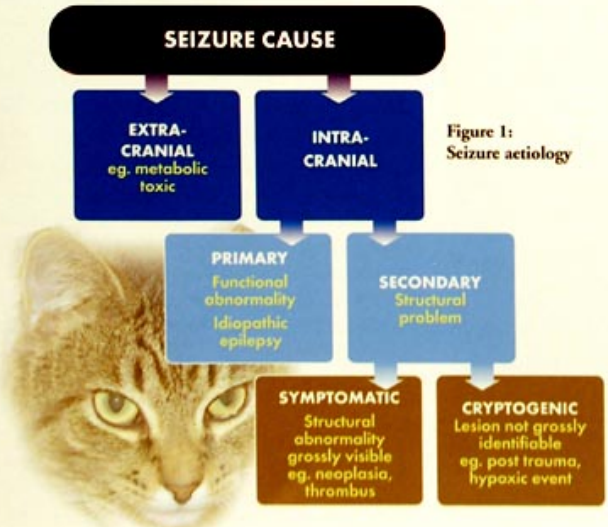


Figure 1: Seizure aetiology

INTRACRANIAL CAUSES OF SEIZURES

Primary disorders are considered to be due to a functional forebrain abnormality. The abnormality is thought to arise at the level of the neurotransmitters and may be due to an imbalance of excitatory (glutamate) and inhibitory (GABA) neuro-transmitters. A genetic basis is suspected, however a lower incidence is recognized versus dogs, likely due to an increased genetic diversity in the cat population. Diagnosis of a primary disorder is reached by exclusion of secondary intracranial and extra-cranial disease, hence the term 'idiopathic' epilepsy.

Secondary disorders are sub-classified into symptomatic (or structural) and cryptogenic disease. Symptomatic causes include congenital disease (e.g. hydrocephalus, lysosomal storage disorder), neoplasia (primary or metastatic), inflammatory disease, cerebro-vascular disease (thromboembolic, haemorrhagic e.g. secondary to hypertension or coagulopathy), infectious disease (e.g. FIP, FeLV, FIV and toxoplasmosis). Although the cryptogenic category sounds vague, it includes several possible causes of seizures including head trauma (immediate or due to scar formation), post-encephalitic seizures and undetectable hypoxic or vascular episodes post anaesthesia or birth.

A recent study reported that symptomatic disease was the most common diagnosis in a population of cats referred with seizures, accounting for 50% of the cases. A further 25% of the cats had idiopathic epilepsy, 22% were diagnosed with reactive causes and 3% were actually due to cardiac syncope *(Schrieft et al, 2008)*. There was no difference in the form of seizure and underlying aetiology (i.e. generalised versus partial). Cats with idiopathic epilepsy were presented at a younger age (median 3 years) and had the longest survival times (median 37 months).

Stages of a seizure: Having confirmed that a paroxysmal event is a seizure, it is useful to establish the behaviour and effects of the seizure upon the patient. Typically three distinct phases are described:

1. ***Aura/pre-ictal period:*** *often associated with excitability, restlessness, anxiety or changes in behaviour.*
2. ***Ictus period:*** *actual seizure.*

3. ***Post-ictal period:*** *recovery phase during which the patient may have residual neurological deficits which often resolve e.g. blindness, ataxia.*

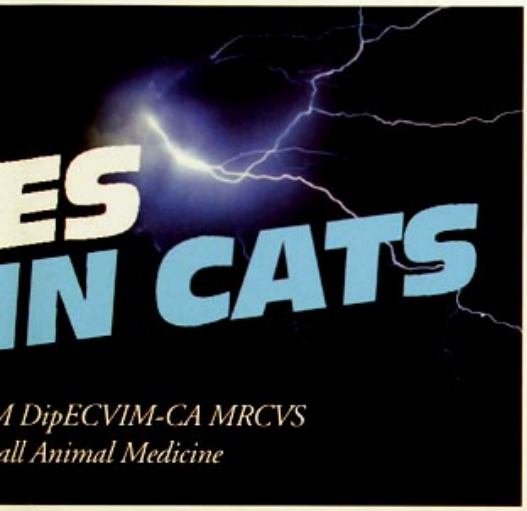
DIAGNOSTIC APPROACH TO THE SEIZURING PATIENT

For the patient presenting in status epilepticus, the immediate priority will be to halt seizure activity before a full history or physical examination can be performed. Once seizure activity has been controlled, a thorough history should be taken.

History.

Particular attention should be paid to:

- The seizure event - obtaining a detailed description or video footage of the event is invaluable, particularly to exclude other causes of episodic events such as syncope. The severity and duration of post-ictal effects, time of day, duration of seizure and relation to any events (e.g. feeding in hepatic encephalopathy) should be established.



- Age of onset of seizures e.g. consider congenital anomalies in cats presenting <1year age e.g. hydrocephalus, lysosomal storage disease and portosystemic shunts.
- Previous medical or surgical history including any current therapies.
- Any known history of trauma or toxin exposure.
- Diet - is the cat fed a complete balanced diet?
- Vaccination history.
- Household - single versus multicat.

Physical examination.

A complete physical examination may give clues to an underlying disease process for example where a patient appears jaundiced or if there are signs of hypertensive retinopathy. The examination should also be complemented by a full neurological examination to look for any other neurological deficits. Typically neurological examinations need to be repeated in cats, to establish the reliability of any abnormalities; most cats tolerate only a very short period assessing neurological function, after which point it can be tricky to know whether any changes are real or are actually due to the cat not wanting to be examined! This is also relevant if the cat is presented in the post-ictal phase, since transient neurological deficits are not unusual in this period. An ophthalmic examination may provide useful clues, for example signs of chorioretinitis in FIP or papilloedema where there is raised intracranial pressure. A normal neurological examination is expected in the inter-ictal period of patients with idiopathic epilepsy.

Diagnostic testing.

In the emergency setting a limited database can provide a significant amount of information rapidly, and exclude many causes of reactive seizures. This would usually include assessment of the PCV, total protein, glucose, electrolytes (sodium, potassium, chloride, calcium) +/- acid-base if available. Once seizure activity is controlled, further diagnostics can be performed according to the historical information, physical examination findings and often owner finances. This may include the following tests

- Complete blood count and biochemistry (especially to assess hepatic, and renal parameters).
- Urinalysis to allow full interpretation of biochemistry results.
- Thyroxine if 8years+ or there are signs suggestive of hyperthyroidism.
- Bile acid stimulation test.
- Blood pressure measurement.
- Infectious disease testing - retrovirus and Toxoplasma gondii serology (IgG and IgM), coronavirus serology.
- Imaging of the thorax and abdomen - to search for evidence of neoplasia, infectious or inflammatory foci and examine the hepatic architecture and vasculature.
- Advanced imaging of the brain (MRI) +/- CSF analysis (cytology, culture and serology) this is considered once reactive causes and systemic disease have been excluded.

THERAPEUTICS

Management of status epilepticus.

The drug of first choice to halt seizure activity is ***diazepam,*** a benzodiazepine. This is rapidly absorbed across the blood brain barrier, with effects seen within 2-3minutes. When administered intravenously, diazepam produces transiently high serum and brain concentrations of the drug, however it has a short duration of action and is not a definitive treatment for status *(Platt 2008).* A dose of 0.5-1mg/kg IV is recommended and the dose can be repeated to effect (to a maximum dose of 20mg) or twice within one hour. Per rectum administration can also be used if IV access cannot be obtained. Intramuscular absorption is unreliable. Adverse affects include respiratory depression, hypotension and sedation. Diazepam should not be used for long term management of seizures; the oral form has been associated with a fatal idiosyncratic hepatotoxicity *(Centre et al, 1996).*

Midazolam is an alternative to diazepam, with the additional benefit of rapid absorption via the intramuscular route. It can also be administered IV or per rectum. A recommended dose is 0.2-0.3mg/kg.

It is essential that any treatable metabolic abnormalities are addressed at this stage for example hypoglycaemia, hypocalcaemia or hyponatraemia. Supportive care in the form of oxygen and intravenous fluid therapy is indicated. If seizure activity has been prolonged and there are signs of increased intra-cranial pressure mannitol therapy should also be considered.

Should seizure activity persist following 2 or more doses of benzodiazepine, longer-acting anticonvulsant therapy should be introduced. ***Phenobarbitone*** is used in this setting, however due to the long period of time taken to reach therapeutic levels with oral dosing, the patient should receive a loading dose of the parenteral form. This is easily obtained and a relatively cheap preparation (as 60mg/ml or 200mg/ml). Given intravenously the drug takes approximately 20-30 minutes to cross the blood-brain barrier. It is recommended therefore that 2-3mg/kg doses are given every 30-60 minutes until a total dose of 12-18mg/kg is reached. This will cause profound sedation and possible respiratory and cardiovascular suppression. Close monitoring (of respiratory and cardiovascular parameters - at the level usually given to an anaesthetised patient) and supportive care are required (turning, thermoregulation, IV fluids, urinary catheter placement). Some patients may require tracheal intubation and ventilation during this period.

Patients that continue to seizure whilst initiating ***phenobarbitone*** loading are considered to have ***refractory status epilepticus.*** In this scenario, if an underlying cause has also been identified and treated appropriately (e.g. hypocalcaemia), additional anti-convulsant therapy will be required. In this situation the patient will need a high level of care, suited best to an intensive care setting. A constant-rate infusion of propofol is used commonly at the Feline Centre (rates of 0.1-0.6mg/kg/min). The patient is usually maintained under heavy sedation for a few hours with gradual tapering of the infusion by 25% every 2hours. The drug is rapidly cleared and can be titrated to effect however concerns exist that repeated administration can lead to Heinz body haemolytic anaemia.

Inhalational anaesthesia is a last resort for refractory status epilepticus where propofol infusion is not available. The care and monitoring required will be similar to that for a patient receiving a propofol CRI. Parenteral ***levetiracetam*** may be a useful adjunct therapy option in the future; current clinical trials are evaluating the efficacy of this treatment in this setting.

MAINTENANCE TREATMENT

Phenobarbitone is the treatment of choice for long-term therapy. An initial starting dose of 2.5mg/kg PO BID is recommended. Dose adjustment should be based on measurement of therapeutic levels. Simultaneously haematology and biochemistry (including dynamic bile acid measurement) should be performed to monitor for adverse effects which include hepatopathy, blood dyscrasias, and dermatitis. Transient side-effects include polyuria, polydipsia and polyphagia.

Levetiracetam *(Keppra ™)* is a newer anti-convulsant that has been used as an effective adjunctive therapy to phenobarbitone *(Bailey et al, 2008).* The mechanism of action is not fully understood, however it is known that the drug is well absorbed and has a short half-life, necessitating 8 hourly treatment. A dose of 20mg/kg PO TID is recommended *(Carnes et al, 2008).* Side-effects include transient inappetance and lethargy, however this is rarely seen. Serum levels can be measured at the Animal Health Trust.

Potassium bromide is no longer recommended in feline patients due to the discovery that up to 45% of cats develop idiosyncratic allergic pneumonitis with treatment *(Boothe et al 2002).*

Other new anti-convulsants include gabapentin, zonisamide and topiramate, however at this time there is limited published information regarding their use.

Determining the efficacy of therapy requires continued monitoring and recording of any further seizure events by the owner. The aim of therapy is to reduce the frequency of seizures by a minimum of 50%. Most patients can be managed with phenobarbitone, however if this provides inadequate control (once appropriate serum levels are reached), levetiracetam is recommended for adjunctive therapy.

Indications for Maintenance Therapy

- When the frequency of seizures is > every 6months (generalised or focal)
- Following cluster seizures or status epilepticus
- When seizures occur following trauma
- If the patient has a structural disorder

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Welcome to Sam Taylor *the new Fort Dodge Feline Fellow*

Sam graduated from the Royal Veterinary College in 2002 and went on to complete an internship at Davies Veterinary Specialists. After a period in practice she returned to referral work at Dick White Referrals before becoming the Feline Advisory Bureau Senior Clinical Training Scholar in Feline Medicine in 2006. She gained the RCVS certificate in Small Animal Medicine in the same year and became a diplomat of the European College of Internal Medicine and a European Veterinary Specialist in Internal Medicine in October 2009. Sam has always been interested in feline medicine and is excited at the prospect of completing research into infectious disease during the next year as this is one of her interest areas, along with feline lymphoma and senior cat health. Having always been 'cat mad' Sam currently owns 3 moggies including an ex-blood donor, Bruno, enjoying a well earned retirement, Eric a hardened hunter of all small things and Boo, a rather too well fed Siamese cross who is in charge of cats and humans alike.

ABSTRACTS

Evaluation of predictors of the development of azotaemia in cats

R.E. Jepson, D. Brodbelt, C. Vallance, H.M. Syme, J. Elliott
J Vet Intern Med 2009; 23, 806-813

Chronic kidney disease (CKD) is a commonly diagnosed condition in the geriatric feline population. It has been suggested that 15% of cats over 15 years of age may have evidence of renal impairment and the prevalence of CKD appears to be increasing. Azotaemia may only be detected when 75% of functional kidney mass is lost. Previous studies have shown that the magnitude of azotaemia and proteinuria are significantly associated with the survival of cats with CKD. In humans, low-molecular-weight proteins and N-acetyl-B-D-glucosaminidase (NAG) – a urinary enzyme that indicates tubular damage - have been investigated as biomarkers for early identification.

The aim of the study was to assess the prevalence of development of azotaemia within 12 months of presentation in a population of geriatric healthy cats and to assess clinical biochemical and urinalysis variables as risk factors for development of azotaemia.

Cats ≥ 9 years of age that were perceived as healthy by their owners were enrolled and returned for repeat examination every 6 months. Systemic hypertension was not an exclusion criteria but the subsequent management of these cats differed from normotensive cats. Cats were followed for a period of 12 months and monitored until the development of azotaemia (defined as plasma creatinine concentration > 2.0 mg/dl).

One hundred and eighteen cats had been followed or reached a study end point by 12 months. Fifteen cats were hypertensive at study entry and treated with amlodipine besylate. The median age was 13 years (11-15 years). The predominant breeds were domestic shorthair (n=83) and domestic longhair (n=15), followed by Persians (n=13). The most common clinical findings were dental disease (60%), palpable thyroid goitre (26.3%), low grade systolic heart murmur with no evidence of heart failure (11.9%), and skin disease including flea infestation (9.3%). At entry 31.4% of cats had a USG ≤ 1.035. Of the 15 cats with systemic hypertension, 9 (60%) had evidence of choroidopathy.

Sixty-six cats remained non-azotaemic at 12 months, of which 8 were treated hypertensive cats. Azotaemia was diagnosed in 30.5% of cat, of which 5 were treated for hypertension. Three previously normotensive cats had developed systemic hypertension during the study period but remained non-azotaemic. Hyperthyroidism was diagnosed in 8.5%.

At study entry, hypertensive cats had significantly higher urine albumin/creatinine ratios and plasma urea concentrations, and significantly lower plasma potassium concentrations and USG than normotensive cats. There was no significant difference in baseline biochemical variables for non-azotaemic cats at the entry into the study and at 12 months. Biochemical data comparing azotaemic cats at the entry and at development of azotaemia showed significant increases in plasma creatinine and phosphate concentrations and significant decreases in USG, body weight and PCV.

The NAG index was positively correlated with USG and UAC and therefore included in the multivariable analysis with other measures for proteinuria. In the final model, only plasma creatinine concentration with either UP/C or UA/C remained significantly associated with the development of azotaemia.

This was the first study to prospectively evaluate and follow a cohort of non-azotaemic geriatric cats and identify biochemical and urinalysis variables at entry into the study that were indicative of the development of azotaemia. Thirty percent of cats developed azotaemia within the 12 months study period, but only plasma creatinine with a measure of proteinuria (UP/C or UA/C) were found to be predictors of the development of azotaemia. Cats with lower USG at entry into the study were also significantly more likely to become azotaemic. Four cats in the study developed azotaemia and clinical signs consistent with CKD but maintained their urine concentrating ability, but this may have resulted from a different underlying pathology. There was no difference in the prevalence of developing azotaemia between normotensive and hypertensive cats.

The NAG index was positively correlated with proteinuria and cats that developed azotaemia but appears to have no major additional benefit to the measurement of proteinuria in predicting the development of azotaemia. In the multivariable model, UP/C (3.505; 95% CI: 1.479-8.304) had a substantially higher OR than plasma creatinine ratio (1.061; 95% CI: 1.019-1.105) and was in previous studies also shown to be significantly associated with decreased survival of cats with CKD and systemic hypertension.

Radiographic abnormalities in cats with feline bronchial disease and intra-and interobserver variability in radiographic interpretation: 40 cases (1999-2006)

J. Gualbois, M.-A. d'Anjou, M. Dunn, K. Alexander, G. Beauregard, J. D'Astous, M. de Carufel, L. Bonton, G. Beauchamp JAVMA 2009, 234(3), 367-375

Feline bronchial disease, also known as feline asthma or allergic bronchitis, is an important cause of respiratory distress in cats. The condition is believed to involve a genetic predisposition, to a type 1 hypersensitivity reaction to inhaled allergens that results in airway inflammation, airway smooth muscle contraction, and excessive mucus secretions. Typically, cats are presented with recurrent episodes of coughing. Feline asthma is a diagnosis of exclusion and radiography is an important component of the diagnostic investigation. The most common radiographic finding is a bronchial lung pattern however other radiographic features such as an unstructured interstitial and alveolar pattern, hyperinflation and hyperlucency, lobar atelectasis and structured soft tissue opacities attributed to the presence of mucus plugs and eosinophilic granulomas have been described. The aim of this study was to determine the prevalence of various radiographic abnormalities in cats with feline asthma and to evaluate intra- and interobserver variability in radiographic interpretation.

Cats were eligible if a final diagnosis of asthma based on history and thoracic investigation had been made and high quality radiographs were available. Radiographs of age and body weight matched cats that did not display respiratory tract abnormalities were selected as controls. Bronchial pattern was described as absent to severe and ill-defined or well-defined. Focal and interstitial patterns were described as focal or diffuse and as uniform or heterogeneous. Other radiographic abnormalities were recorded. Ratios of lung inflation were calculated for each cat. Intra- and interobserver agreement and diagnostic accuracy were assessed.

A bronchial pattern was assigned in 37 (93%) cats and was classified as mild in 53%, moderate in 50% and severe in 10%. An unstructured interstitial pattern was seen in 30 (75%) cats, which was diffuse in the majority of cats (n=28). Bronchial wall mineralisation was identified in 25 (63%) cats. Nodular, tubular or amorphous soft tissue opacities were observed in 11 (28%) cats, and 8 of these 11 cats had a moderate or severe lung pattern. Ill-defined hyperlucencies were seen in 21 (53%) cats and a flattening of the diaphragm in 31 (78%) cats. Atelectasis (n=19; 48%), bronchiectasis (n-7; 18%), mild cardiac changes or vascular changes (n=7; 18%) were also identified.

Bronchial wall mineralisation was detected in 21 of the 40 control cats, and the presence was not significantly associated with age.

The lung field width ratio (width of lung field at T7 divided by T7 and maximal width of lung field divided by the width of T7) was significantly higher in cats with feline asthma.

Intraobserver agreement was good but interobserver agreement between the examiners was variable. For most examiners, significant associations were found between examiner diagnosis (correct versus incorrect), level of examiner certainty, and bronchial pattern severity. Cats with minimal bronchial changes and bronchial mineralisation were more likely to be miscategorised. On the other hand, examiner certainty increased for radiographs of cats with moderate to severe changes.

The results of this study suggest that a bronchial pattern is the most common radiographic finding in cats with feline asthma, followed by an unstructured interstitial pattern and signs of lung hyperinflation. The prevalence of the bronchial pattern which is typically attributed to bronchial wall thickening secondary to inflammatory infiltrates and local oedema was in this present study with 93% higher than in previous studies (59%-90%). Disease severity and chronicity of the study population may have been responsible for this.

Bronchial wall mineralisation was observed in many cats with feline asthma (25/40; 63%) but it was also common in control cats (21/40; 53%). Bronchiectasis was thought to be a rare consequence however it was detected in 18% of the study population and may be underestimated. Twenty-eight percent of cats had nodular, tubular, or amorphous pulmonary soft tissue opacities. These are most likely the result of unstructured interstitial or alveolar infiltrates, granuloma formation or mucus plugs. Cats has to be taken as such opacities could be easily be mistaken for primary or metastatic neoplasms.

The results of this study demonstrated that examiner diagnosis and level of certainty in the diagnosis were both associated with severity of a bronchial pattern regardless of the level of experience of the individual examiner. Therefore, a diagnosis of feline asthma must rely on clinical and laboratory findings as well as results of thoracic radiography.

Temporal changes in characteristics of injection-site sarcomas in cats: 392 cases (1990-2006)

S.C. Shaw, M.LS. Kent, I.K. Gordon, C.J. Collins, T.A. Gresley, L.A. Beckett, G.M. Hammond, K.A. Shorrocks JAVMA 2009, 234 (3), 376-380.

An association between vaccine injections and development of sarcomas has been suggested, with fibrosarcomas being the most common type of tumour to develop at injection sites. These tumours are highly invasive and require radical surgical excision. Radiotherapy may be necessary to obtain control in the case of recurrence. In the US, a task force was established to identify methods of prevention and treatment of these tumours. Recommendations were to administer the rabies vaccine in the right rear leg as distally as possible, FeLV vaccine in the left rear leg as distally as possible and FVRCP +/- C vaccine in the right shoulder. Prior to the establishment of these recommendations a majority of vaccines were administered in the interscapular region.

This study aimed to assess the change in the distribution of injection-site sarcomas.

Medical records of cats evaluated at the Veterinary Teaching Hospital of the University of California from 1990 through 2006 were retrospectively reviewed for a histologic diagnosis of sarcoma. Information was obtained on signalment, tumour histologic classification and anatomic location. All biopsy reports were reviewed to confirm diagnosis.

Four hundred and thirty cats were identified, but 38 cats were excluded because biopsy reports were not available. The remaining 392 cats fulfilled the inclusion criteria. The mean age was 9.6 years (range 1.4-18.8 years) and 94.4% were mixed-breed cats. There was an equal distribution of males and females. Types of tumours according to the histological diagnosis included 311 fibrosarcomas (79.3%), 71 other soft tissue sarcomas (18.1%), 5 liposarcomas (1.3%), 3 osteosarcomas (0.8%), and 2 chondrosarcomas (0.5%). Most tumours were detected in the interscapular region (n=167; 42.6%), followed by the right pelvic limb (n=61; 15.6%), right thoracic limb (n=30; 7.7%), left pelvic limb (n=30; 7.7%), right lateral aspect of abdomen (n=26; 6.6%), left lateral aspect of the abdomen (n=22; 5.6%), left thoracic limb (n=21; 5.4%), right lateral aspect of thorax (n=20; 5.1%), left lateral aspect of abdomen (n=12; 3.1%), and the tail (n=3; 0.8%).

Before the establishment of the recommendations in 1996, 53.4 % of ISS were detected in the interscapular region and this decreased significantly after 1996, as did the proportion of tumours on the right and left lateral aspect of the thorax. The proportion of tumours that were detected at the right thoracic limb and right lateral aspect of the abdomen increased significantly from 1.1% to 9.5% and 2.2% to 7.9% respectively.

When results for the pelvic limb were combined with those of the adjacent lateral abdominal regions, the tumours on the caudal left side of the body significantly increased from 11.4% to 13.8% and on the caudal right side of the body from 12.5 to 25%. In total, the number of tumours caudal of the diaphragm significantly increased to 39.8% whereas the proportion of tumours found cranial of the diaphragm significantly decreased to 60.2%. In 2003 the number of tumours caudal of the diaphragm surpassed the number of cranial tumours.

The authors suggest the significant decrease in the cranial region coincides with the recommendations on vaccination sites. Tumours on the thoracic wall are most likely due to aberrant placement of the injection destined for the interscapular region. The significant increase of tumours on the abdominal wall may be caused by misdirected injections intended for the pelvic limb. This steady increase is of concern as treatment of tumours on the lateral abdominal wall can be more difficult than in the interscapular region. Complete excision requires abdominal wall resection and estirpation of affected organs. Adjuvant radiation may be challenging because of the vital underlying organs. According to the authors, these tumours originating from the pelvic limb often extend onto the abdominal body wall. Amputation of the affected limb alone may be inadequate in obtaining complete excisional margins.

If ISSs that arise from the limbs and lateral abdominal wall correspond to vaccine recommended for this region, the percentage of tumours caused by injections other than vaccines are negligible; rabies vaccines would be responsible for 51.7%, FeLV for 28.6% and FVRCP +/- C for 19.7% of all ISS detected after 1996 when the recommendations were issued.

There are limitations to this study as is was retrospective in nature and it could not be ascertained that each tumour was truly induced by an injection. The study population may also not be representative of the general population. Despite a decrease in the proportion of interscapular ISS, about 41% of vaccines were reported to have been administered in the interscapular region in 2002. The authors emphasise that misadministration of injections should be prevented as tumour formation at the lateral abdominal wall is of considerable concern and may result in higher morbidity rate due to incomplete surgical excision and inability to treat with radiotherapy.

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Speakers

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