Part One: Anatomy & Diagnosis

ANATOMY OF LENS STABILITY

The lens of the eye sits in the patellar fossa. Although you might have thought this structure to be found in the knee, it is actually the depression in the anterior face of the vitreous that itself is formed by the posterior convexity of the lens. Anteriorly, the lens abuts the iris, which provides it a measure of support. Around the equator of the lens are the lens zonules (or Zonules of Zinn, which form the suspensory ligament of the lens). These zonules anchor the lens capsule to the ciliary body, which is responsible for accommodation or focusing of the lens.

DIAGNOSIS OF LENS LUXATION

Lens luxation is the full dislocation of the lens out of the patellar fossa, either anteriorly (into the anterior chamber in front of the iris) or posteriorly (into the vitreous). Both types of luxation can be surprisingly hard to diagnose, either due to very subtle changes or dramatic changes (e.g., corneal edema from glaucoma) that preclude full visualization of the lens.

Anterior lens luxation with cataract is often very obvious (Figure 1), but when the lens is clear or when corneal edema from glaucoma is present, it can be hard to visualize. One feature to look for in this scenario is the positioning of the iris. Generally, the curvature of the iris (which is

(continued on next page)
allow enough natural iris dilation to observe present, examination in a darkened room with glaucoma. To confirm a diagnosis of lens can also be accompanied by an increase in vitreous in the anterior chamber. Subluxation lens (phacodonesis) or iris (iridodonesis) as (from one side of the lens tilting and pushing an asymmetrically shallow anterior chamber) be very subtle. Signs to look for can include crescent” is the classic sign of lens subluxation (Figure 4).

CAUSES OF LENS INSTABILITY

Lens luxation is known to be of genetic origin in many canine breeds (e.g., Terriers, Chinese Crested, American Eskimo). A slit beam normally convex only because it lies over the lens with the curvature of the cornea. A slit beam can close the filtration angle, increasing IOP and potentially precipitating a glaucoma crisis.

That said, mydriatic agents are sometimes used by ophthalmologists in the management of lens luxation. Examples include when pupillary block glaucoma is present (when the lens is anteriorly located and the pupil is constructed around the vitreous, or when the pupil is tight against the lens like a closed ball valve), attempts to replace an anteriorly located lens with a procedure called “couching,” and in post-surgical (femtomile) management to reduce synechia formation, help with comfort, reduce inflammation of iris vasculature, and potentially precipitating a glaucoma crisis.

In the cat, uveitis is the most common cause of lens luxation, which presumably occurs due to inflammatory breakdown of the lens’ suspensory ligament. Therefore, in cats, an infectious disease workup (FeLV, FIV, FIP, toxoplasmosis, etc.) is important when presented with a lens luxation. An infectious disease (e.g., pyothorax) can close the filtration angle, increasing IOP and potentially precipitating a glaucoma crisis.

Part two will discuss the medical and surgical management of lens instability in the dog and cat. To view part two on our website, please visit angell.org/lensx.

REFERENCES


For more information about Angell’s Ophthalmology service, please visit angell.org/ophtalmology. Dr. Coster can be contacted at 617-541-5095 or ophthalmology@angell.org.
Canine Hyperadrenocorticism

Shawn Kearns, DVM, DACVIM

Canine hyperadrenocorticism (HAC) is an endocrine disease affecting primarily older dogs with 80–95% of cases caused by pituitary-dependent disease (PDD). The remainder is due to an adrenocortical tumor (AT). There is a slightly increased predisposition for females (55–65%), and larger breeds may be affected more frequently with an AT.

We are all familiar with the common clinical signs of HAC as well as laboratory findings, so those will not be discussed in this article. If a single sign compatible with HAC is present, it is likely to be either polyuria/polydipsia or skin coat changes. Less common signs include those related to a macro-tumor (behavior change, inappetence, obtundation, facial palsy, spontaneous thromboembolism), though sometimes signs are subtle. About 15–25% of dogs will develop neurologic signs months to years after the initial diagnosis. Other less common signs include anorexia, tauric atrophy, ligament laxity, facial palsy, spontaneity, pseudo-hypercalcemia and cortisol-induced insulin resistance. Signs from an invasive adrenocortical carcinoma may include hemorrhage due to vessel invasion or thrombosis of the vessel (juxtacortical, hind-limb edema or paraparesis). Less common clinical presentations are identified first, a thorough review of the history, physical examination findings and routine laboratory test results may provide additional evidence for HAC.

A recent Consensus statement was published in the Journal of Veterinary Internal Medicine (JVIM 2017; 27: 1292-1314), so the remainder of this article will focus on the Panel recommendations in regards to testing for HAC. Testing should only be considered if there are clinical signs (common or uncommon). Biochemical panel, complete blood cell counts, urinalysis, UPC and blood pressure results by themselves are not indications to test.

No test is 100% diagnostic for HAC. Diagnosis depends on documenting increased cortisol production (ACTH stimulation) or decreased sensitivity of the hypothalamus/pituitary-adrenal axis (HPAA) to the normal negative feedback of steroids administration (low-dose dexamethasone suppression test, LDST). Reference ranges may need re-evaluation in the future, as we are likely testing sooner and ranges were generated many years ago. If a patient tests negative, repeat testing in 6–12 months may be warranted, especially if signs progress.

The LDST is currently considered the screening test of choice unless urologic HAC is a consideration. The cortisol concentration, at 8 hours after dexamethasone administration, is used to diagnose HAC. In the clinical experience of the Panel, normal dogs are usually below or close to the detection limit of the sample (≤ 0.19). Therefore, if a patient is below 1 but not below the detection limit, HAC may still be considered. In addition, an inverse pattern, where the 8-hour cortisol is high but the 8-hour is below the detection limit, may also indicate HAC. Results should be interpreted with caution if the patient is currently taking phenobarbital, as those dogs occasionally will not show suppression.

The ACTH stimulation test has a lower sensitivity (range 35–95%) so is considered inferior to the LDST as a screening test, but it is the test of choice for urologic HAC. Synthetic ACTH is recommended over compounded drug, and intravenous administration is preferred over intramuscular. Progesterone, glucocorticoids, and ketocortisone all suppress the HPAA axis and response to ACTH. Phenobarbital does not affect the test. The urine cortisol / creatinine ratio (UCCR) is a sensitive test (70–100%) for detection of cortisol hypersecretion but is influenced by endogenous stress and non-adrenal illness. Collection should take place at home, at least 2 days after a veterinary visit, to decrease the likelihood of false positives.

Differentiating tests should only be pursued once there has been a positive on a screening test. The canine ACTH measurement is the most accurate stand-alone biochemical test for differentiation; however, reference ranges vary by technique and certain assays are less sensitive. In addition, proper sample handling is crucial to accurate results. Discontamin results can occur, and many dogs with PDH will have ACTH at the lower end of the reference range, but they should not be lower than the low-end reference range. The high-dose dexamethasone suppression test (HDDST) can be used to differentiate PDH from AT. If suppression occurs, the patient likely has PDH. However, if there is no suppression, it should be kept in mind that about 50% of PDH dogs will not suppress even at the higher dose.

A macroadenoma may be more likely in a dog without an AT that does not suppress on the HDDST.

For those patients who cannot be hospitalized, an oral dexamethasone suppression test can be considered. Samples for UCCR are taken on 2 consecutive days, and then 10 15 hours after dexamethasone (0.4mg/kg PO) are given. At 6-8 hour intervals and urine collected again the following day. A decrease in the UCCR <50% of the mean basal values is consistent with PDH. Lack of suppression does not discriminate between PDH or AT. Changes in metabolism of dexamethasone may influence the results of any of the suppression tests.

Imaging must be used in conjunction with hormonal testing and should not be used as the sole modality for diagnosis. Radiographic changes in patients with HAC include abdominal distention, good contrast due to fat deposition, hepatomegaly, bladder distention, mineralization of the bronchi and pulmonary interstitium, and possibly a mass effect centralization in the retroperitoneal space. On US, adrenal gland width is considered the most informative parameter but breed and body-size related differences must be considered. US can estimate tumor size and possibly vascular or soft tissue invasion; however, CT scan and MRI are more sensitive for evaluation of invasiveness as well as metastases (see Figure 1 and 2). Metastases, veno-venous invasion by a tumor mass, adrenal width (>4cm) or a combination of these findings is highly suggestive of malignancy.

Because radiation therapy or hypophysectomy is the required treatment for macro-tumors, and both are more effective with smaller tumors and in the absence of neurologic signs, the Panel recommends pituitary imaging be considered for all dogs at the time of initial diagnosis (see Figure 3). Of course, if clinical signs suggest a macro-tumor, CT or MRI is also recommended. As pituitary tumors and a cortisol-secreting AT may be present at the same time, some also recommend pituitary imaging with AT.

If a patient does not fit the clinical picture for HAC, testing for occult HAC (“atypical HAC”) should not be considered. While a cause and effect relationship between AT sex hormones and clinical signs is well documented, a causative relationship with sex hormones and PDH has not been established. Therefore, an adrenal sex-hormone panel should be considered for patients with inappropriately low cortisol levels on initial screening tests and with adrenal tumors not testing positive for cortisol secretion. Food-stimulated HAC should also be a differential when considering occult HAC, especially if the fasting cortisol concentration is low.

In conclusion

• Endocrine testing for HAC should only be considered if there are compatible physical exam findings and history. Testing should not be performed based on laboratory changes alone.

• The LDST is considered the screening test of choice.

• An endogenous ACTH level or adrenal ultrasound are recommended for differentiating between AT and PDH.

• Sex-hormone testing is recommended mainly when an adrenal tumor is present and the initial cortisol testing had returned low.

In addition, proper sample handling is crucial to accurate results. Discontamin results can occur, and many dogs with PDH will have ACTH at the lower end of the reference range, but they should not be lower than the low-end reference range. The high-dose dexamethasone suppression test (HDDST) can be used to differentiate PDH from AT. If suppression occurs, the patient likely has PDH. However, if there is no suppression, it should be kept in mind that about 50% of PDH dogs will not suppress even at the higher dose.

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Tooth fractures are a common finding when examining the mouths of cats and especially dogs. Most of these fractures expose the pulp canal of the tooth, leading to tooth death and infection. Unfortunately, most dogs and cats are too stoic for their own good and do not overtly show the pain associated with pulp exposure or subsequent root abscess. It is up to us to detect and properly treat these painful, diseased teeth. If the pulp canal of a tooth is exposed, the only proper treatments are extraction or a root canal procedure; “wait and see” is not appropriate (Figure 1).

Canine teeth (and incisors) are frequently damaged from random trauma (HBC, falls, etc.). The most commonly fractured tooth in dogs is the maxillary 4th premolar. This tooth is most often fractured due to chewing trauma from items like bones (ANY actual bone), non-flexible nylon bones, antlers, hooves, and, a recent addition to the bad chew-toy list, yak’s milk. These products are often advertised as long lasting. Unfortunately, because they don’t break down, the teeth used to chew them, usually the maxillary 4th premolar, do fracture. Since these fractures occur from chewing trauma, rather than random trauma, dogs are likely to fracture both maxillary 4th premolars. A common fracture of the maxillary 4th premolar can be a “slab fracture,” fracturing a significant portion of the buccal surface of the tooth and often extending below the gum line to the root structure (Figure 2). Even if the pulp canal is not exposed, these complicated fractures can make it very difficult to realistically keep these teeth without significant periodontal disease developing. Any damage to any tooth at or below the gum line will increase the periodontal disease. The maxillary 4th premolar is one of the teeth most likely to have calculus buildup, making detection of fractures more challenging. Some of these fractures are subtle, so it is important to know the normal shape of the maxillary 4th premolar. This tooth resembles the number four on its side (Figure 3).

The commonly accepted classic sign of an abscessed tooth is facial swelling. Unfortunately, the vast majority of abscessed teeth do not form these externally visible swellings. It can take years, if ever, for the chronic infection to destroy enough bone in the right direction to form a visible swelling. More common is the formation of intermittent draining tracts as the root abscesses go through cycles of forming and draining. These are called gumboils, or purules (or parasites), and are visualized as pink/red bumps on the gum line. They represent the openings of chronic draining tracts from tooth root abscesses and are at the mucogingival margin of the affected tooth (Figures 4 and 5).

Fractures of deciduous teeth are also often neglected with the idea that the tooth will eventually fall out anyway. Normal exfoliation (loss) of a deciduous tooth is due to resorption of the root by odontoclasts present in the tissue above the crown of forming, unerupted permanent tooth. Any pulp-exposed tooth is a highway for infection. At the end of this highway of infection of a fractured deciduous tooth, is the forming, unerupted adult tooth. Proper formation and eruption of the permanent tooth can be affected. The deciduous tooth will indeed eventually fall out, but due to erosion of the root and supporting structures from infection. I consider fractured deciduous teeth to be an urgent problem, and they should be extracted promptly to prevent damage to the underlying permanent tooth (Figures 6 and 7).

All too often, our patients suffer silently with abscessed teeth. As we head into National Pet Dental Month, don’t miss the opportunity to spot these teeth and treat them properly or, even better, educate clients on what NOT to give their dogs to chew and prevent the majority of tooth fractures.
PATHOLOGY

Diagnosis of Multiple Myeloma: Bence-Jones Proteins

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DEFINITION AND PATHOPHYSIOLOGY
Bence-Jones proteins, also referred to as M-proteins, myeloma proteins, paraproteins and free immunoglobulin light chains, are a component of immunoglobulin produced in excess by B-cell-derived clonal cell populations. The specific immunoglobulin component is unassociated kappa or lambda light chains. Multiple myeloma, and some extramedullary plasma-cell tumors and chronic B-cell lymphocytic leukemia, can produce Bence-Jones proteinuria. Multiple myeloma is a clonal proliferation of malignant plasma cells, typically arising in the bone marrow, that produce an immunoglobulin or component of immunoglobulin. Because of their small size (MW=22,000-44,000), Bence-Jones proteins can readily pass from the blood through the membrane into the urine. Bence-Jones proteins were named after the English physician Henry Bence Jones, who described their ability to precipitate when urine is heated to 45ºC, then redissolve when urine is further heated to near boiling.

CONSIDERATIONS FOR DIAGNOSIS OF MULTIPLE MYELOMA
Two of the four following criteria are generally required for diagnosis of multiple myeloma:

• Radiographic evidence of osteolytic bone lesions
• >20% plasma cells in bone marrow aspirate or biopsy specimens (Figure 1)
• Demonstration of monoclonal or biclonal gammopathy with serum electrophoresis
• Demonstration of Bence-Jones proteinuria

More than 50% of dogs and cats with multiple myeloma may have light-chain proteinuria. A diagnosis of multiple myeloma cannot be excluded based on a negative Bence-Jones protein result for the following reasons: 1) secretion may be intermittent or the concentration too low to be detected in a single urine sample; 2) myeloma cells may be secreting intact immunoglobulin molecules rather than free light chains; and 3) non-secretory types of multiple myeloma (rare) do not produce Bence-Jones proteinuria.

LABORATORY TESTS FOR BENCE-JONES PROTEINS
Bence-Jones proteins are not detectable via protein electrophoresis of urine. Detection of Bence-Jones proteinuria requires sophisticated tests, such as urine protein electrophoresis, immunoelectrophoresis and immunofixation electrophoresis. The screening test most commonly used is urine protein electrophoresis.

SAMPLE REQUIREMENTS FOR URINE PROTEIN ELECTROPHORESIS
Sample used of urine in a sterile leak-proof container or red-top (serum) tube on ice packs is acceptable. An early morning urine collection is ideal. Remember to include the method of collection and date/time of collection on the submission form. The urine sample should be kept refrigerated prior to shipping, since the proteins are stable at refrigerator temperature (2-8ºC) for approximately one week or can be stored frozen at -8ºC for up to one month.

INTERPRETATION OF TEST RESULTS
A positive test result will appear as a monoclonal spike in the ß or Y protein regions on urine protein electrophoresis. It is important to remember that a negative test result does not exclude a diagnosis of multiple myeloma or B-cell neoplasia, and a positive result requires additional confirmatory testing. Causes of abnormal test results are presented in Table 1.

CONFIRMATORY TESTS
A positive Bence-Jones protein result on urine electrophoresis can be confirmed and further characterized by more sensitive and specific techniques, such as immunoelectrophoresis and immunofixation electrophoresis. Immunofixation electrophoresis distinguishes between kappa and lambda light chains and identifies the heavy chains of IgG, IgM and IgA. The most common problem reported with immunofixation electrophoresis is that it also detects intact immunoglobulins in the urine that are unassociated with Bence-Jones protein. Additional diagnostic tests that may be helpful in confirming a diagnosis of multiple myeloma include serum protein electrophoresis to evaluate for monoclonal or biclonal gammopathy, radiography to evaluate for osteolytic lesions and bone marrow cytology to evaluate for plasma cytosis (Figure 1).

TABLE 1

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<tr>
<td><strong>POSITIVE RESULT</strong></td>
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<td><strong>NEGATIVE RESULT</strong></td>
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<tr>
<td>Multiple myeloma</td>
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<tr>
<td>Extramedullary plasmacytoma</td>
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<td>Other B-cell derived neoplasms, such as chronic lymphocytic leukemia</td>
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<tr>
<td>Chronic lymphocytic proteinuria</td>
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<td>False Positive:</td>
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<td>• Marked proteinuria</td>
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<tr>
<td>• Kappa or lambda interference</td>
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<td>• Hemoglobin interferences from (hemorrhage or hemolysis)</td>
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For more information, please contact Angell’s Pathology service at 617-541-5014 or pathology@angell.org.

REFERENCES

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NEW ANTI-DIARRHEA DRUG, CROFELEMER

STUDY TO INVESTIGATE THE CLINICAL EFFICACY OF A NEW ANTI-DIARRHEA DRUG, CROFELEMER

The drug is an anti-secretory compound that has shown promise in treating diarrhea without affecting intestinal motility. Animals accepted into the study will receive up to $4,000 for all costs of treatment and testing.

To qualify, vaccinated and parvo-free dogs must be between a months and 16 years of age, have watery diarrhea without blood or mucus, and can not be on Metronidazole, Albenza, probiotics, Antibiotics (Ciprofloxacin, Sulfadimethoxine (Aldrin), or Flagyl.

To enroll a patient, please call Jen McManus in Angell’s Internal Medicine service at 617-541-5138 or email jmcmanus@angell.org for further directions. To learn more about this study, including eligibility requirements, please visit angell.org/lymphoma.

ANGELL INTERNAL MEDICINE - FUNDED CLINICAL STUDY TO INVESTIGATE THE CLINICAL EFFICACY OF A NEW ANTI-DIARRHEA DRUG, CROFELEMER

ANGELL ONCOLOGY - FUNDED CLINICAL TRIAL FOR T-CELL LYMPHOMA IN DOGS: FREE FLOW CYTOMETRY AND BIOPSY

Prior to enrollment all patients will have samples taken for lymph node biopsy and flow cytometry to confirm T-cell phenotype at no cost to the owner. Once the dog is confirmed eligible (non-indolent, T-cell lymphoma), all procedures and treatments required by the study including chemotherapy, anti-body therapy, exam, bloodwork, and other required diagnostics will be fully funded.

To enroll a patient, please call Dr. Ivan Martinez for further directions. To learn more about this study, including eligibility requirements, please visit angell.org/lymphoma.
Laparoscopic Ovariectomy and Gastropexy

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OVERE is most commonly performed completely through two small 5-mm incisions in the abdomen (one just caudal to the umbilicus and one midway between the umbilicus and pubis). A wound-sealing device is used to achieve hemostasis of the ovariectomy and to maintain the peritoneal cavity. Security seams and subcutaneous layer closures are performed using nonabsorbable suture material.

Surgery can be performed via laparoscopic-assisted technique in order to prevent life-threatening GDV occurring. This minimally invasive surgical technique can be performed at any time during a dog’s life and is highly recommended to be performed at the same time as a spay or neuter in a predisposed dog. One study evaluated none of the dogs that had laparoscopic gastropexy performed developed GDV and all had good attachments visualized at ultrasound follow-up. The overall goal of a laparoscopic gastropexy is that it is a very easy technique to perform, it produces a permanent attachment between the stomach and the right abdominal wall, it does not alter gastric function, and it has minimal complications. Also, this very minimally invasive technique may save a pet’s life by preventing GDV, as well as presenting a very effective and stress-free life-threatening event.

Ovariectomy and gastropexy can be performed at any age and are most frequently performed simultaneously. Gastropexy can also be performed at the same time as a routine castration for male dogs and only involves one small mid-abdominal incision and a right-sided 5-cm incision in the skin. Another common recommended laparoscopic technique is laparoscopic cryptorchidectomy. This can be performed for unilateral or bilateral cryptorchid dogs. Lastly, laparoscopic surgery is a fantastic technique for ovarian remnants. Patients with presumptive ovarian remnants benefit immensely from this surgery because of increased visualization and magnification, as well as the less invasive technique with an excellent prognosis. Postoperative recovery from laparoscopic surgery has been proven to be faster, less painful and less costly compared with a routine celiotomy. Patients routinely stay overnight for pain management and monitoring and are discharged the following day. They are rested for about 10-14 days with feeding and then returned to normal routine. They have much smaller incisions and less swelling and pain than traditional surgery patients. At Angell, we strive to deliver the most advanced medical care available to our veterinary patients—the same that would be offered to patients in human medicine. We are fortunate to be able to offer many minimally invasive techniques for our pets, which have been proven to be less painful, invasive and have faster recoveries than more traditional techniques.

References


For more information about Angell’s Surgery service, please visit angell.org/surgery. Staff can be reached at 617-541-5048, or by emailing surgery@angell.org or surgery@angell.org.
We mail one complimentary copy of our newsletter to each of our referring partners. Please circulate this copy within your practice.

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Please call 781-902-8400 to book appointments or referrals, or visit angell.org/waltham for a full list of expanding Waltham services.

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