Brain Tumors

How Technology has Shifted the Paradigm of Brain Tumors in Veterinary Medicine

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As the technology available to veterinary medicine evolves, this month we review how some of the most recent advances in the 21st century have drastically changed the management of one of the most devastating diagnoses to the owners: brain tumors…and why, even when you can’t win the war, certain battles are worth being fought...

Seizures in geriatric patients (underlying causes) – Trouble in paradise

New onset seizures and behavior changes in geriatric dogs (>7YO) are frequent reasons for consultation in small animal practice. Behavior changes can include staring into space, pacing around the house, compulsive circling, decreased responsiveness to stimuli coming from one side only (hemineglect), bumping into things despite normal vision, or more radical changes in personality (such as friendly dogs becoming aggressive). Both seizures and behavior changes — once systemic/metabolic causes have been ruled out — point to a forebrain/cerebral cortex disorder.

As for younger adult dogs, the differentials for seizures include idiopathic/cryptogenic, neoplasia, inflammatory, vascular, trauma, degenerative, and infectious. Epilepsy (which does not necessarily mean idiopathic) is defined as an enduring disorder of the brain that is characterized by recurrent seizures. The term cryptogenic epilepsy is used frequently in the older population, as it refers to recurrent seizures with no obvious underlying cause identified after complete work-up (i.e. in a way, it could be just a late onset of “idiopathic” epilepsy, but the term cryptogenic specifies that an occult/hidden cause is suspected but has not been found). Structural epilepsy refers to recurrent seizures due to a structural forebrain lesion (e.g. granulomatous meningoencephalomyelitis [GMEM], brain tumors).

New onset seizures >7YO
• Physical and Neurological examination
• Asymmetrical neurological deficits or not
• Co-morbidities?

Rule out extra-cranial causes (CBC/chemistry, minimal database)
• e.g. hypoglycemia

Cryptogenic epilepsy
• ~20%
• treat as "idiopathic"

Structural epilepsy (i.e. Forebrain lesion)
• ~70-80%
• e.g. meningiomas, gliomas, strokes, GMEM
• treat underlying cause + seizures
• seizures may resolve

Other causes of reactive seizures
• e.g. head trauma, intoxication
• treat underlying cause + seizures
• seizures may resolve

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The second storm of our winter season was so ominously forecast that Governor Cuomo actually closed the LIE in anticipation of the need to plow it clear before allowing vehicles back on. Turned out to be less of a problem than forecast, fortunately, so little interruption in travel took place. We are elated to share the “glad winter’s over” feeling with most Long Islanders; happy to put our snow blowers away and look forward to warmer days and spring’s colors.

A few years ago, the NY Times contained an article entitled “Good or Bad, Medical Scans Cost the Same”. With the current health care controversy front page news, consumers need to be aware that older scanners both CT and MRI, are not equivalent to modern units. Considering MRI scanners, newer 3 Tesla units have a higher magnetic field strength and an improved signal to noise ratio thereby providing more precise resolution. The 3 Tesla unit at LIVS is the most advanced in veterinary medicine. Because of our custom Philips installation, it is capable of allowing the patient to undergo a complete body scan at one sitting, reducing time under anesthesia, yet still providing the highest resolution available anywhere. The NY Times also stressed that expertise in interpreting scans is of equal import. Our neurology/neurosurgical service has become the most active service in the country, and the experience garnered from that gives LIVS expertise that is unmatched. Our neurology/neurosurgery services are available 24 hours a day-all year for emergencies.

On March 21st, another of the “Owner Conversation Series” was held to provide the general practice veterinarian with “bullet pointed” talking points to help distill complex veterinary concepts into relatable conversations with owners regarding diagnostic and therapeutic options as well as post-operative care. Members of the LIVS Neurology Department were present in this conversational based discussion offering personal insight and individual perspectives preserving the intimate nature of this series and provided ample opportunity for dialogue. Held at “Season’s 52” in Garden City, it was quite successful. In addition, the LIVS Neurology Team also discussed “What should we be telling owners about Seizures?”. Members of the staff participated in the annual “St. Baldrick’s” event, a non-profit foundation which stands in solidarity with kids fighting cancer, raising money to find cures. This volunteer-driven charity funds more in childhood cancer research grants than any organization other than the U.S. government.

LIVS is currently hosting a fourth year veterinary student from The Ohio State University, College of Veterinary Medicine, Ms. Alida Mataczynski, who is doing a rotation in Dr. John Sapienza’s department of Ophthalmology.

Dr. Curtis Dewey, associate professor and section head of Neurology/Neurosurgery at the College of Veterinary Medicine at Cornell is at LIVS regularly for consultation as is our animal behaviorist, Dr. Sabrina Poggiagliolmi. Appointments can be made at 516-501-1700.

Again, we welcome your comments e-mailed to lmarino@livs.org

Leonard J. Marino, MD, FAAP, LVT
Brain Tumors

Continued from Front Cover

Examination and minimal database
Any new onset seizure in dogs >7YO justifies at least a visit to the veterinarian, with a detailed neurological examination and a minimal database. A recent study in this category of the canine population revealed that, in contrast to dogs with earlier onset seizures, only ~20% had a diagnosis of cryptogenic epilepsy, with ~80% suffering from structural epilepsy (with brain tumors as the most common underlying cause). A full minimum database (CBC/Chemistry, urinalysis, +/- thoracic radiographs and abdominal ultrasound) should be obtained, with serial neurological examinations. If no obvious extra-cranial cause is identified (e.g. hypoglycemia, hepatic encephalopathy), advanced diagnostic imaging should be considered, especially if asymmetrical neurological deficits are present (e.g. menace response, nasal sensation or postural reaction deficits).

The naked truth about MRI magnets: Yes, size DOES matter...
In the last decade, high field MRI (>1.5 Tesla) has become more widely available to veterinary patients. Although low-field MRI (<1Tesla) remains available, high field/ very high field MRI offers major advantages for imaging of the veterinary patients:
- The higher signal-to-noise ratio obtained with a 3T MRI allows for a shorter anesthetic time, specifically relevant in brachycephalic or geriatric patients, often affected by impaired cardiac function or other comorbidities.
- The magnetic field produced by a 3T MRI is more homogeneous, resulting in markedly improved image quality. This is specifically relevant for masses that are deemed surgically removable, as the MRI images directly guide the surgical planning (see Figure 1 and Figure 2).
- Susceptibility artifacts are increased with a 3T MRI, which allows for detection of smaller lesions and micro-hemorrhages that would remain otherwise undiagnosed with a lower field MRI (see Figure 3).
- Improved detection of contrast-enhancement: this allows for the use of a lower dose of intravenous contrast agent, specifically relevant for patients with impaired kidney function.

Brain tumor: the elephant in the room
The combination of high field MRI and CSF analysis may sometimes only narrow down the list of differentials to a couple of etiologies

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Figure 1: Post-contrast 3T MRI images in the dorsal (a) and sagittal (b) planes of a large, ill-defined intra-axial mass affecting the frontal lobes and creating a mass effect (the mass is outlined in red) in a 10 year old Husky. The hyperintense (bright) signal allows the surgeon to visualize the outline of the lesion to be removed during surgery. The use of FFE sequence (c) enhances inhomogeneity in the magnetic field created by hemoglobin, and allows detection of “signal void”, appearing dark/black in the transverse plan (red star). This is especially important for the neurosurgeon, as the lesion is now suspected to bear significant neovascularization, or intratumoral hemorrhage, and surgery can be planned accordingly. Based on this information obtained by the 3T MRI, surgical removal of the mass via a transfrontal craniectomy was performed with the use of the CUSA® used at LIVS (d), to allow gross total resection and ease the hemostasis during surgery. Histopathology of the mass presented on MRI and removed surgically was consistent with hemangiosarcoma. A complete work-up did not identify hemangiosarcoma in any other location, leading to the diagnosis of a primary brain hemangiosarcoma. Recovery from surgery was uneventful; the patient received adjunctive chemotherapy post-surgery, with post-surgical survival of 1 year. This is the first report of long-term successful removal of a brain hemangiosarcoma in veterinary medicine. The CUSA excel system, seen in close-up view (e), increases the extent of resection of brain tumors while preserving the surrounding normal brain tissue. Transfrontal craniectomies are performed for masses located in the olfactory bulbs or frontal lobes, and are usually associated with excellent cosmetic results once the patient hair has grown back. The patient is presented here in immediate post-operative period (f); another example is visible with this 11 year old Boston Terrier (g), presented also in immediate post-operative/recovery period, after transfrontal craniectomy for removal of a frontal lobe oligodendroglioma.

Figure 2: Post-contrast 3T MRI images in the dorsal (a) and sagittal (b) and transverse (c) planes of the brain of a 12 year old DSH presented for 1 month of behavior changes and right hemiparesis. The neurolocalization was consistent with a left forebrain lesion. On 3T MRI, a very large contrast-enhancing (bright) mass is seen compressing the left temporal, occipital and parietal lobes. The 3T MRI shows very distinct margins/limits between the mass (red star) and the brain parenchyma, by opposition to the mass shown in Figure 1 a and b. This MRI aspect is very typical of meningioma in cats, and surgical removal was recommended. Complete tumor resection was performed through a left rostrotentorial craniectomy. This type of surgery is usually associated with rapid post-operative neurological improvement, as seen for this patient in the immediate post-operative period (d). Recovery from surgery was uneventful; the patient was discharged 4 days post-surgery and neurological examination remains normal 2 years post-surgery.
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Lorine A.

“My dog did very well with the collar, and it kept her away from the incision.”
Smith C.
(e.g. inflammatory granuloma VS neoplastic mass), but it will often allow a presumptive diagnosis to be established (see Figures 2, 3 and 4). If a mass-like lesion is identified in a surgically reachable area of the forebrain, the different management options should be discussed thoroughly with the owners. As technology improves and renders manageable pathologies once deemed untreatable, the push from owners to be made aware of all options rises. Therefore the general practitioner’s knowledge should allow him/her to discuss these options. The location and MRI aspects of the lesion greatly impact the preferred management option: conservative management, minimally invasive biopsy, surgical debulking from partial resection (<50% of the mass expected to be removed) to gross total resection (no residual tumor visible under the surgical microscope). Radiation therapy remains an option for masses located in areas judged non-surgical.

**Surgical planning**

The improvements made in neuro-imaging (e.g. 3T MRI) not only directly impact surgical planning through better image quality, but the recent addition of neuronavigation to the arsenal of the veterinary neurosurgeon has greatly shifted the paradigm of brain tumor management in veterinary medicine. Through use of MRI guided neuronavigation system, such as the BrainSight® system used at LIVS (see Figure 4), the neurosurgeon is no longer condemned to “guess” the extent of a lesion by the best use of his own visual cortex, but can nowadays rely on a precise, real-time tool allowing him to virtually “navigate” the brain of the patient before and during the procedure. This also allows for planning of safer surgical corridors ahead of a potential craniectomy, whether it being for a simple biopsy, or anticipated gross total resection.

**Surgical technique – Do NOT bring a knife to a gun fight**

As in human neurosurgery, craniotomies/craniectomies are not in their infancy anymore in veterinary medicine. Dr. Harvey Williams Cushing (1869-1939) pioneered various approaches to the brain a century ago and, in the veterinary world, the craniectomy techniques described by Hoerlein and Oliver more than 30 years ago remain to this day the first step of any intracranial procedure.
Dr. Gazi Yasargil, in the second half of the 20th century, drastically changed the outcome of intracranial neurosurgeries in humans, by introducing magnification in the operating room (OR), through the use of surgical loops and surgical microscope. More recently, magnification systems have become more user-friendly, and less cumbersome, facilitating their use in an OR setting. The VITOM® HD system used at LIVS is the only equipment of its kind dedicated to veterinary neurosurgery on Long Island (see Figure 5). Defined as an “exoscope”, it combines a high definition camera recorder (1080p) with the magnification power of a high-end surgical microscope, allowing the entire surgical team (neurosurgeon, assistant/resident, anesthetist) to follow the procedure in real time on a flat screen HD TV. This was recently shown to be associated with an excellent outcome in veterinary neurosurgery as it allows better visualization of the nervous tissue, reduces surgical fatigue for the surgeon and improves operative flow.

“Vision without action is merely a dream. Action without vision just passes the time. Vision with action can change the world.”

In regards to visualization, other parts of the surgical procedure have greatly benefited from technological advances. It is now common knowledge that extent of tumor resection is correlated to patient prognosis in human glioblastoma management. This need for maximal resection (ideally gross total resection) to achieve better prognosis is also reflected in veterinary medicine, with well encapsulated tumors such as feline meningiomas being associated with median survival of up to 3 years post-surgical resection. Although canine meningiomas can have infiltrative margins with normal brain tissue, the use of a surgical aspirator (such as the Cavitron Ultrasonic Surgical Aspirator [CUSA®] system used at LIVS) has been associated with longer survival times than those achieved with traditional surgery alone or even traditional surgery combined with radiation therapy (one study reports a median survival time of >1200 days). This specific piece of equipment generates ultrasonic waves to produce tissue cavitation and “cut out” brain tumor without damaging the surrounding healthy brain tissue. It also provides irrigation and aspiration for debris removal, all in one surgical tip (see Figure 1).

Adjunctive therapies – post-surgical strike warfare

Multimodal management remains the gold standard in many veterinary oncology cases, and neuro-oncology is no exception to the rule. The use of chemotherapy agents such as hydroxyurea, usually very well tolerated in dogs, has been shown to improve survival time. Furthermore, new strategies in neuro-oncology, such as immunotherapy, have finally given the neurosurgeon the upper hand in brain tumor management. A canine meningioma vaccine was recently developed at the University of Minnesota. This protocol, recently used at LIVS, allows 90% of the dogs treated to not develop recurrence after surgery (basically aligning the behavior of canine meningiomas with their feline counterpart), and has been associated with a median survival time of 645 days, almost three times that of of historical controls.

In summary, options are available for the management of brain tumors in veterinary medicine in 2017, and public awareness is growing. Despite all technological improvements however, the key point of early recognition of symptoms, diagnosis and treatment cannot be emphasized enough, as many wars are easier to win before the opponent reaches full strength...
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What is the adrenal medulla and how does it work?
The adrenal gland is made up of an outer adrenal cortex and inner adrenal medulla. The adrenal medulla is a modified sympathetic ganglion and part of the nervous system. Its primary cell is the chromaffin cell which produces and stores a variety of neurotransmitters including the catecholamines. The catecholamines (predominantly epinephrine, but also norepinephrine and dopamine) are pre-made and stored in cytoplasmic vesicles. They are expelled by exocytosis when the adrenal medulla is stimulated by nervous impulses. Synthesis of all catecholamine starts off as the amino acid phenylalanine. Through a complex pathway phenylalanine gets converted to dopamine then norepinephrine and eventually epinephrine. This pathway is subject to negative feedback by norepinephrine. The half-life of circulating catecholamines is a few minutes. Both norepinephrine and epinephrine are rapidly broken down to multiple metabolites such as normetanephrine and metanephrine.

What are pheochromocytomas?
Pheochromocytomas are malignant tumors of the adrenal medulla. They are often incidental findings and are extremely variable in appearance with unpredictable growth, metastasis and local infiltration patterns. They are usually solitary but bilateral has been reported and they can range in size from 0.5cm to 10cm. Secretion of catecholamines is not initiated by nervous impulses but instead is episodic and random. Stimulation can occur in response to physiologic stressors such as hypotension, hypoglycemia, hypoxia and stress as well as manual manipulation during surgery. Drugs such as metoclopramide and steroids may also enhance stimulation. The normal negative feedback loop that regulates catecholamine production is nonfunctional in these tumors and the pathway continues without a stop mechanism.

What are the clinical signs of pheochromocytomas?
Patients with pheochromocytomas are typically middle aged to older. There is no reported breed or sex predisposition. Due to the nature of pheochromocytomas, the clinical signs and exam findings they produce are variable. They can range from no clinical signs or include weakness, syncope, tachypnea, gastrointestinal disturbances, restlessness, depression, tachyarrhythmias, systemic hypertension, acute blindness, and polydipsia.

How are pheochromocytomas diagnosed?
There are no consistent complete blood count, serum chemistry or urinalysis findings. Occasional non-specific findings include leukocytosis due to stress and circulating catecholamines, increased liver enzymes secondary to hypertension or alterations in hepatic perfusion, hyperglycemia secondary to catecholamine induced glycogenolysis and gluconeogenesis, proteinuria from hypertensive glomerulopathy and hypostenuria from catecholamine induced inhibition of vasopressin.

Abdominal radiographs can sometimes show a mid-abdominal mass but abdominal ultrasound is frequently needed to localize the mass to the adrenal gland. On ultrasound, it is most common to see a singular adrenal mass with a normal contralateral gland, though there can occasionally be bilateral adrenal gland masses (not necessarily of the same etiology). While ultrasound can detect invasion of the vena cava and phrenicoadominal vein or tumor thrombi, it cannot distinguish between pheochromocytomas and other types of adrenal masses (adenomas, nodular hyperplasia, adrenocortical carcinomas, granulomas, etc.). Abdominal CT Scans can
also be used to localize abdominal masses but face the same diagnostic limitations as ultrasound. We do not perform guided aspirates of adrenal masses due to the risk of massive catecholamine release and precipitation of a hypertensive crisis.

The gold standard for diagnosing pheochromocytomas is histopathology. If histopathology is not to be performed, or if a presumptive diagnosis is desired before surgery, plasma or urine catecholamine and metabolite measurements can be performed. Dogs with pheochromocytomas have higher concentrations of plasma free metanephrine and normetanephrine than healthy dogs and those with nonadrenal illnesses. Urine catecholamine to creatinine ratios are also frequently used to diagnose pheochromocytomas with urine normetanephrine measurement having the highest sensitivity and specificity. One caveat to catecholamine measurement is that stress in any patient causes increases in plasma and urine catecholamines and metabolites. It has been shown that less stress occurs at home and therefore the preferred sample for evaluation is urine collection that took place at home!

Serum inhibin measurement is a newly available test for evaluating adrenal gland tumors. Inhibin is a glycoprotein synthesized in ovarian granulosa and testicular Sertoli cells and suppresses follicle stimulating hormone release from the pituitary gland. The adrenal glands are extranodal sources of inhibin. In neutered dogs with adrenal gland tumors, adrenocortical tumors and pituitary dependent hyperadrenocorticism are associated with increased serum inhibin whereas undetectable inhibin is highly supportive of a pheochromocytoma.

How are pheochromocytomas treated?
Adrenalectomy is the treatment of choice however this is not always performed for medical reasons (i.e. vascular invasion, metastatic disease), financial limitations or owner preference. Chemotherapy and radiation therapy risk precipitating hypertensive crises, have little success in human patients and have not been truly evaluated in veterinary patients.

The basis of medical management is alpha adrenergic blockade to decrease the actions of excessive catecholamines. This treatment does not stop local invasion or metastasis but can help control certain clinical signs. The goal of alpha blockade is to correct chronic vasoconstriction and allow expansion of plasma volume. It is also used as a pre-operative treatment in those patients that do go forward with surgery. Phenoxybenzamine is the non-selective alpha blocker of choice and acts by non-competitively and irreversibly binding to alpha receptors. The reason non-competitive phenoxybenzamine is the drug of choice is that a surge of catecholamines cannot override its inhibition as it can with competitive agents (i.e. Prazosin, Tamsulosin). Dosing starts at 0.5mg/kg q12 and can increase to 1-2mg/kg. If used pre-operatively it should be given for at least two weeks prior to surgery. Studies have shown that dogs pre-treated with phenoxybenzamine have a significantly decreased mortality rate compared with untreated dogs.

Additional medical management involves beta blockade if the patient also suffers from tachycardia or tachyarrhythmia. Options include propranolol 0.2-1mg/kg q8 or atenolol 0.2-1mg/kg q12-24. If beta blockade is needed, it is very important to always use an alpha blocker first for at least one week. Patients can develop severe hypertension if alpha-1 vasoconstriction is allowed to act unopposed by beta 2 mediated vasodilation.

There is one report of a dog with an inoperable pheochromocytoma being treated with 1-131 labeled metaiodobenzylguanidine. Metaiodobenzylguanidine(MIBG) has a structure similar to norepinephrine and can be taken up by pheochromocytomas. When labeled with a beta emitter such as I-131 this can be used therapeutically. This technique has a 33-60% partial remission rate in people and may be a possible treatment for veterinary patients some day in the future.

What is the prognosis for patients with pheochromocytomas?
Overall prognosis for pheochromocytomas depends on size, metastatic disease, local invasion, perioperative complications, and concurrent disease. It is typically guarded to good if there is no metastatic disease after surgery with reported survival rates one to two years. The prognosis is poor if metastatic disease is present no matter the treatment. Reportedly 50% of dogs with adrenal medullary tumors eventually develop concurrent tumors originating from endocrine glands like pituitary, adrenal cortex, thyroid gland, parathyroid gland and pancreatic beta cells. There is no information on prognosis with medical management only.

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<th>Receptor</th>
<th>Major Effector Tissues</th>
<th>Major Functions</th>
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<tr>
<td><strong>Alpha</strong></td>
<td>SM, sphincters</td>
<td>Contraction (constriction),</td>
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<td><strong>Alpha</strong></td>
<td>Nerve endings</td>
<td>↓ Transmitter release</td>
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<td><strong>Beta</strong></td>
<td>Cardiac muscle, Kidney</td>
<td>↑ Heart rate and force, ↑ Renin secretion</td>
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<td><strong>Beta</strong></td>
<td>SM including bronchi, Liver, Skeletal muscle</td>
<td>Relax SM ↑ Gluconeogenesis, glycogenolysis ↑ Glycogenolysis and K+ uptake</td>
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<td><strong>Beta</strong></td>
<td>Adipose</td>
<td>↑ Lipolysis</td>
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<td><strong>DA</strong></td>
<td>SM especially renal, mesenteric and cardiac</td>
<td>Relax renal vascular SM (higher doses activates β1 and α1 receptors)</td>
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