Central vs. Peripheral Vestibular Diseases

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Most people can recognize signs of vestibular dysfunction. It is hard to miss a dog with a persistent head tilt or a cat circling in one direction. However, your job is not yet done! It is important to further localize vestibular dysfunction to central or peripheral as this will markedly alter your differential list and have significant impact on your conversation with the client.

Vestibular anatomy

The vestibular system is a special sensory system. The receptors are located within the petrous temporal bone inside the calvarium. There are three crista ampullarae, one at the end of each semicircular canal. These receptors detect rotational movements of the head in 3 planes. Associate with the semicircular canals are the utriculus and the sacculus which both contain receptor organs called the macula. These receptors detect linear acceleration and static head position. The signals from these receptors are transduced and transmitted through the vestibular nerve.

The vestibular nerve travels to the medulla where it synapses on four vestibular nuclei. This happens bilaterally. Further projections from the vestibular nuclei include

1. Descending medial longitudinal fasciculus
2. Ascending medial longitudinal fasciculus
3. Vestibulospinal tract
4. Vestibulocerebellar tracts
5. Pathway to the vomiting center

The descending medial longitudinal fasciculus (MLF) allows projections from the vestibular nuclei to synapse on motor neurons that innervate the cervical musculature via facilatory input (increase muscle tone). The ascending MLF synapses on the oculomotor nuclei so that they eyes move with the head when turned. This relay is what is known as the oculocephalic reflex. The projections via the ascending MLF cross over so that vestibular nuclei have projections to oculomotor nuceli bilaterally. The vesbitulospinal tracts are motor tract that project from the vestibular nuclei. The nuclei are gait generating nuclei and the vestibulospinal tract transmits these signals to the limbs to activate gait. They are facilitory to ipsilateral extensors and inhibitory to contralateral extensors. There are sensory projections into the cerebellum and inhibitory projection *from* the cerebellum that synapse back on the vestibular nuclei. All of the information exchanged between vestibular nuclei and the cerebellum passes through the caudal cerebellar peduncle. Lastly there are projections from the vestibular nuclei to the vomiting center. Hopefully, it becomes obvious how alterations in these pathways lead to clinical signs of vestibular dysfunction that we label as “vestibular disease”.

NB: Vestibular disease is not a disease. There are many diseases that cause vestibular signs. If you label a patient as “vestibular” you have not made a diagnosis. You have localized the lesion, albeit only partially.

Peripheral vestibular signs

Peripheral vestibular signs result from any lesion affecting the vestibular nerve, the receptors, or the structures that house the receptors. Clinical signs may consist of vestibular ataxia, positional ventrolateral strabismus, ipsilateral head tilt, and nystagmus in the direction away from the lesion (run away!). These animals should not exhibit signs of weakness. Ipsilateral Horner’s syndrome or facial nerve paresis/paralysis may occur in some since the sympathetics to the head and the facial nerve pass through the inner ear.

Otitis interna is by far the most common cause of peripheral vestibular signs in both dogs and cats. It usually develops from local extension of a middle ear infection, but animals do not always have signs of otitis externa. Polyps in cats can cause peripheral vestibular signs and predispose them to otitis media/interna. Diagnosis is usually by otic exam. An empirical course of action for first time offenders is reasonable. Don’t forget to look for systemic causes of things that predispose to ear infection, such as food allergy or poor hygiene. Repeat or chronic cases however will need additional work up. Radiographs are useful to document bony change to the bulla that would be consistent with chronic infection. When infection has led to lysis or sclerosis of the bullae, surgery (bullae osteotomy) is often needed. Both surgeons and neurologists will advocate for advanced imaging to confirm the problem and rule out other concurrent issues. Medical management consists of cleaning with saline and a long course of antibiotics (4-6 weeks), ideally based on culture obtained via myringotomy. Generally the prognosis for recovery is good but residual head tilts are possible.

Idiopathic vestibular disease (this is the one time it is appropriate to use vestibular and disease together) is the second most common cause of peripheral vestibular signs. In dogs it presents acutely and is non-progressive. These dogs can be so markedly ataxic that it can be hard to assess their postural reactions or determine if the lesion is central vs peripheral. However, when you are able to test them they are ALWAYS NORMAL. Geriatric vestibular disease is NEVER central. In cases that are difficult to assess you have the option to refer immediately for advanced imaging. These are older patients and clients may wish to be certain sooner rather than later that signs are not a result of a tumor or stroke. Alternatively, you can manage the dog supportively for a day or two and rule out

other common causes of peripheral vestibular signs. Supportive care with IV fluids and anti-nausea medication may buy you some added time to reassess the patient and better determine if the lesion is central or peripheral. Most dogs begin improving in about 72 hours but can take several weeks to fully recover. Residual head tilts are not uncommon.

Cats are also affected with idiopathic vestibular disease but have a bimodal distribution (young and old). Signs are often bilateral and seem to occur more frequently when the seasons change from warmer to cooler and vice versa. Bilateral peripheral vestibular signs have some unique clinical findings. These animals have bilateral vestibular ataxia. As a result they will often obtain a crouched, wide based posture and sway side to side. Because they have no sensory input about head position, when they try to move their head they do so slowly and with wide excursions. Again, because this is peripheral, postural reactions are normal. The lack of bilateral sensory input also means they have no oculocephalic reflex. The only other time we see a decreased oculocephalic reflex is with brain swelling. So how do you know not to panic? The rest of your exam of course! Animals with elevated intracranial pressure will have abnormal postural reactions, abnormal cranial nerves, and are not very likely to be walking around and interacting appropriately as one would with bilateral peripheral signs.

Congenital vestibular signs have been reported in numerous breeds of dogs and cats. Signs are typically present at birth or arise within a few weeks of life. There is a variable association with deafness. Diagnosis is typically based on clinical signs and age. Most of these animals improve over time. Deafness, if present, will not.

Hypothyroid may cause signs of peripheral or central vestibular dysfunction. Signs may be acute or chronic. The mechanisms have not been confirmed but are thought to be due to either myxedema of the vestibular nerve or some functional change. Diagnosis can be tricky since these dogs are usually older and with co-morbid disease. A full thyroid profile including T4, free T4, TSH and thyroid antibodies should be done. Treatment with thyroxine supplementation carries a good prognosis.

Technically anything placed in the inner ear can lead to ototoxicity and peripheral vestibular signs. It may be safe to use topical otic medications when vestibular signs are not present, but I would certainly avoid them in the face of vestibular signs. Some systemic medications can damage the hair cells within the receptors and lead to peripheral vestibular signs. Aminoglycosides are the most well described, but toxicity has also been observed with cisplatin, furosemide, and salicylates. Unfortunately, damage is usually permanent but compensation may occur over time.

Central vestibular signs

Central vestibular dysfunction may *look* peripheral, but peripheral vestibular dysfunction will never look central. The most reliable clinical sign of central vestibular dysfunction is proprioceptive deficits, which are ipsilateral to the lesion. Other signs may include vertical nystagmus or nystagmus that changes direction, other cranial nerve deficits, and a head tilt that can be towards or away from the lesion. Lesions of the vestibular nuceli will cause an ipsilateral head tilt. Lesions of the cerebellum, will cause a contralateral head tilt. This is because the cerebellum has an inhibitory influence over the vestibular nuclei and the loss of inhibition is what causes the head to be pushed in a paradoxical direction.

Common causes of central vestibular dysfunction include brain tumors (especially meningioma), vascular accidents, and infections/inflammatory disease. An MRI and CSF are generally needed to make a diagnosis. If advanced imaging is not possible, history and signalment can help narrow your differential list. Blood tests are available to document active infectious disease processes or you can treat empirically for the most common infectious diseases that cause inflammatory CNS disease. This would include Rocky Mountain Spotted fever, ehrlichia, anaplasma, toxoplasma, and neospora. Fungal infections of the brain stem are less common but possible. If empirical therapy fails and you are unable to obtain a definitive diagnosis via advanced diagnosis, immunosuppression for immune-mediated inflammatory may be considered in certain patients.

Unfortunately, most causes of central vestibular dysfunction carry a more guarded prognosis and/or require more expensive treatment such as brain surgery or radiation therapy. Regarding vascular accidents, prognosis depends on whether the lesion is ischemic or hemorrhagic, how large it is, and if there is an underlying cause. About 50% of canine stroke patients have an identifiable underlying etiology. Common risk factors include hyperadrenocorticism, chronic kidney disease, hypothyroidism, diabetes mellitus, and hypertension.

Hypothyroidism, while a risk factor for ischemic stroke, can lead to signs of central vestibular dysfunction in absence of an identifiable lesion on MRI. This is thought to be related to some functional injury in the central vestibular system. These patients do not improve until thyroid supplementation is provided. Treatment usually results in resolution of clinical signs.

Lastly, metronidazole toxicity can result in clinical signs of central vestibular dysfunction. Signs are typically acute and may be associated with higher doses or longer duration of therapy. Signs will resolve when the medication is discontinued. Administration of diazepam (0.5 mg/kg IV once then PO q8h for 3 days) will resolve signs more quickly. This is thought to be due to displacement of metronidazole at the receptor level.

Suggested reading

	Peripheral	**Central**
Head Tilt	Ipsilateral (severe)	Variable
Nystagmus	Fast phase **away**, does not change	Changes with position, vertical, any
Postural reactions*	Normal	Ipsilateral
Cranial Nerve	VII – ipsilateral	V-XII
Horner's Syndrome	Often	Rare

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Conservative Management of IVDD: When the Money's Just Not There

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Disc disease is a surgical disease. A generally recommend advanced imaging and surgery for patients suspected to have Hansen type I disc degeneration and acute herniation, regardless their level of dysfunction. Decompressive surgery provides a faster and more complete return to function with a decreased risk of recurrence. However, because of finances, this is not possible for every patient.

Intervertebral disc disease causes neurologic signs referable to the spinal cord that are graded. A variety of injury scales have been described. The grading scale I use is as follows and comes from Sharp and Wheeler 2005.

- Grade 1 Pain only
- Grade 2 Pain, ataxia +/- paresis
- Grade 3 Pain, nonambulatory paresis
- Grade 4 Pain, paraplegia
- Grade 5 Pain, sensory negative (loss of deep pain)

Not included on the scale is loss of voluntary control of urination. This begins to be lost around the same time as weakness develops. I generally assume that a patient that cannot walk of his/her own free will, cannot urinate of his/her own free will either. This will have important management implications and should be discussed thoroughly with the client.

Acute spinal cord injury resulting in grade 3 dysfunction, is a surgical emergency until proven otherwise. It is important to speak with clients directly about the implications of delaying surgery in these cases. For painful and ambulatory dogs, surgical referral is on a next available and urgent basis respectively. I still think it is wise to have painful patients schedule an appointment with a specialist for 1-2 weeks after their initial evaluation with the family veterinarian. This is so that if they fail to improve, the appointment is in place and emergency fees can be avoided. If they improve, it is easy enough to cancel the appointment several days in advance.

When referral is not an option, management will depend on the severity of clinical signs. In all cases of suspected type I disc herniations, absolute, strict rest for two weeks is essential. This allows any tear in the annulus to heal and prevents additional disc material from herniating.

Grade 1

Dogs with back pain as their only clinical sign have the best chance (~95-100%) of responding to conservative therapy. Dogs with neck pain do not seem to respond quite as favorably, but failure of response does not always lead to further neurologic deterioration. This is because there is more room in the cervical spinal canal allow the spinal cord to move away from the rupture disc rather than get compressed between the disc and the 'wall' of the spinal canal. These patients can become markedly painful and refractory to medications which may prompt an emergent referral.

For cases of extreme back or neck pain when referral is not an option, the next best treatment would be hospitalization with parenteral opioids and/or other analgesics (lidocaine, ketamine). Opioids can be administered intermittently or as a continuous rate infusion combined with analgesic with different mechanisms of action. If finances are such that even placing a catheter is too costly, an initial IV dose of an opioid followed by SQ dosing in hospital can be done. If hospitalization isn't possible, a single injection can be given in hospital. You may also consider placing a transdermal fentanyl patch in these patients. It will take several hours to reach therapeutic levels, but will last up to 3 days.

Patients that are going home on pain management can be started on tramadol as their parenteral opioids lose effect. For hospitalized patients, tramadol may be added as continuous rate infusions are slowed or when patients begin to eat while on injectable medications.

Anti-inflammatory medications may also beneficial. Non-steroid and steroid medications cannot be given together and deciding between the two is primarily individual opinion. However, administration of dexamethasone is a known contra-indication in recumbent patients with spinal cord injury (Levine et al. 2008). Additionally, if you think there is any chance a client will change his/her mind about referral, I would not use steroids. Carprofen is available for SQ and oral administration; this makes it a good choice for patients who are too painful to eat or who are hospitalized for parenteral pain management. If you choose to manage a patient with a steroid, appropriate doses MUST be administered. Anti-inflammatory doses of prednisone are 0.5-1 mg/kg/day.

Additional oral analgesic medications can be prescribed as needed. Options include gabapentin, amantadine, and methocarbamol. I have found the muscle relaxants typically benefit patients with visible muscle fasciculation more than those without. Acupuncture and laser may benefit some patients and can be used as alternatives if oral medications are not tolerated.

Grade 2

Dogs with pain and ataxia only have reasonably good response rates to conservative therapy (85-90%), though recurrence may be an issue. Unless these dogs are intensely painful, there is not additional justification to hospitalize them. If patients are discharged on oral medications and strict rest, they should be re-evaluated in ~48 hours to assess response to therapy. If all is well, the next assessment should be in 2 weeks. At this time, if the patient has improved, physical rehabilitation may be considered. Avoidance of high impact activity is recommended long term.

Failure to respond to treatment or worsening while on treatment should prompt referral. As stated previously, dogs with suspected type I disc herniations should have referral discussed at the initial appointment. For dogs that worsen and referral is not an option, alternative plans as described for each neurologic grade can be implemented.

Grade 3

These are dogs that I would recommend hospitalizing, regardless of their level of pain on initial evaluation. Because these dogs are non-ambulatory, most clients aren't going to be able to tell if they get worse overnight or not. Ideally I would recommend hospitalization for 48h so you can assess response to therapy. Response rates with conservative therapy approach 75-85%.

Hospitalizing these dogs also allows you to more accurately determine their voluntary bladder control and provide manual evacuation (via expression or urinary catheter) if needed. If you are managing a grade 3 dog who *does* need manual bladder expression, catheterization might be ideal to avoid increasing their pain when you attempt bladder expression. Indwelling or intermittent catheterization is appropriate since the most significant risk factor for development of urinary tract infection in dogs with thoracolumbar type I IVDD is duration of bladder management and not method of bladder evacuation (Bubenik and Hosgood 2008). Manual expression is least expensive. However, if expression is difficult medications may be needed. An alpha-antagonist such as prazosin (alpha-1 antagonist) or phenoxybenzamine (non-selective alpha antagonist) helps relax the urinary sphincter and facilitate expression. If abdominal wall tension or resistance from the patient is a problem diazepam can be added for skeletal muscle relaxation. Bethanechol is a cholinergic that increases detrusor tone but should NOT be used in the face of an upper motor neuron bladder to avoid urinary bladder rupture.

If patients are static or improved enough to go home after 48h of hospitalization, recheck exam and urine culture, even if manual evacuation wasn't needed, should be done in 2 weeks. Remember that clients should adhere to strict confinement during these two weeks and patients should be carried out to urinate/defecate. No wandering/dragging around trying to find the right spot. These patients should have a well-padded, confined space. Clients should alter the pet's position every ~4-6h to avoid development of bed sores. If the patient has a tendency to urinate in the crate, absorptive padding should be used.

If hospitalization is not an option, follow the analgesic plan as appropriate according to pain level and finances. Teach the client how to palpate the bladder and express if the patient doesn't urinate at least twice daily. Recheck these patients in 48 hours and adjust the plan if needed. Additional recheck should happen every 2 weeks until the patient's status stabilizes and medications can be reduced. For patients that do not regain the ability to walk, monthly urine cultures should be performed initially. If no infection is detected, the frequency of monitoring can decrease. During the recheck physical examination look for decubital ulceration or signs of self-mutilation that you may need to address.

If you prefer anti-inflammatory doses of steroids, consider the side effects when managing recumbent dogs. Polyuria/polydipsia that occurs with steroid administration leads to frequent soiling. This may mean more frequent bladder expressions and/or bedding changes. Additionally, steroids increase risk of cutaneous infections and urinary tract infections in recumbent patients already predisposed to decubitis and UTI.

Physical rehabilitation should be avoided in the first 2 weeks. Passive activities may begin after that but active activities (walking) should not be initiated til >4 weeks into treatment and only if the patient is improving and comfortable.

Grade 4

Paraplegic dogs should be managed as described above for grade 3. However, these dogs are far more likely to need manual bladder evacuation (manual expression or urinary catheterization). It is important to be able to recognize overflow incontinence in these patients and not to mistake it for voluntary urination. Up to 60-80% of dogs that can feel their digits will regain the ability to walk with conservative therapy (versus >95% with surgery). They are likely to have residual deficits and a high rate of recurrence (>50%) or the development of chronic secondary problems and complications (decubital ulcers, urinary tract infection).

If these patients do not regain the ability to walk, a cart can be considered to increase quality of life. Cart fittings can be done 4 weeks into treatment if the patient is still non-ambulatory. Introduction and adaptation to the cart should be added gradually. Bladder expression may still be needed and is a key factor to address with clients when discussing long term implications of managing a paraplegic at home. Difficulty expressing the bladder at home and/or chronic monitoring and urinary tract infections are frequently the cause for euthanasia.

Grade 5

If sensation to the digits is lost, odds of recovery of deep pain are <5%. If they do not regain sensation, voluntary ambulation will not happen. Some of these dogs may develop reflex walking known as spinal walking. Spinal walkers do not have voluntary control over their urination and will still require long term, daily manual evacuation. This is a key point to discus with clients who have severely affected pets. These dogs generally end up in carts if they are not euthanized and do not develop myelomalacia.

Grade 5 dogs are at risk of developing myelomalacia (10%), or ascending and descending necrosis of the spinal cord. This process is not reversible and can be delayed in onset (up to ~5 days AFTER the initial injury). It is indistinguishable from spinal shock in the acute period. For this reason, I recommend longer initial hospitalization or daily rechecks if hospitalization is not an option. Dogs with myelomalacia are extremely painful and will have an ascending panniculus (cutaneous trunci) reflex. If deficits develop in the thoracic limbs as result of ascending necrosis into the cervical intumescence, euthanasia is recommended. In rare cases, I have seen myelomalacia ascend partially and not affect the thoracic limbs. These patients never recover and are typically left with flaccid paralysis that cannot sustain spinal walking. Spinal shock appears initially as flaccid paralysis but quickly evolves into spastic paralysis and then recovery.

High dose methylprednisolone use (30 mg/kg bolus followed by twenty three hours of infusion at 5.4 mg/kg per hour) in acute spinal cord injury is **controversial** at best and if used, should be administered within 8 hours of injury. I am not a proponent of this treatment method due to the overall lack of demonstrable benefit and known risk of increased complications and side effects. However, in dire straits I have discussed therapy for acute and rapidly progressive grade 4-5 dogs. Dexamethasone is not a substitution for methylprednisolone. The beneficial effects of high dose methylprednisolone are not thought to be related to glucocorticoid activity, which is 10 times as potent in dexamethasone compared to prednisone.

Suggested reading

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Neurolocalization of Intracranial Disease

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The brain is divided into 5 major anatomic areas and each area may be associated with one or more cranial nerves (CN).

- Telencephalon – cerebral cortex, no direct cranial nerve association, CN I
- Diecnephalon – thalamus, CN II (optic nerve)
- Mesencephalon – colliculi/midbrain, CN III (oculomotor nerve) and CN IV (trochlear nerve); the red nucleus is located here
- Metencephalon – cerebellum and pons, CN V (trigeminal nerve)
- Myelenceophalon – medulla, CN VI (abducens), CN VII (facial), CN VIII (vestibulocochlear), CN IX (glossopharyngeal), CN X (vagus), CN XI (spinal accessory), CN XII (hypoglossal)

*Note that together the telencephalon and diencephalon are known as the prosencephalon or forebrain.

If you are able to assess cranial nerve function and know the origin of the nerve you are testing, it is relatively easy to figure out where the problem is. The most common mistake I see in those learning to perform the neurologic exam, is that subtle abnormalities are missed or written off as examiner error. Pay attention to subtleties! I myself have ignored subtle abnormalities and have been proven wrong. The second most common mistake I see, is not examining the cranial nerves altogether. Pin-pointing lesion localization helps us prioritize our differential list and have a realistic conversation with the clients.

Cranial nerves are peripheral nerves that either terminate or originate in the brain. A lesion can affect a cranial nerve from within the brain or along its periphery. The former will typically also cause postural reaction deficits. If a lesion is rostral to the red nucleus, postural reaction deficits will be contralateral. If a lesion is caudal to the red nucleus, postural reactions will be ipsilateral. We are all aware of the difference between central vestibular signs and peripheral vestibular signs, but these differences are true for central versus peripheral disease of other cranial nerves as well. Vestibular signs get special attention because they are often more apparent without physically touching the pet and are often hard to miss rather than hard to identify.

Gait assessment

Gait assessment is the first part of every neurologic exam. The brain is responsible for gait *generation* and gait *coordination.* Gait generation is akin to starting the engine of a car. If the engine doesn't start, the car doesn't go anywhere. If the engine starts slowly or weakly, the car may go a little ways then stop; it would appear paretic. Gait coordination would be like the drive shaft of a car, it allows the wheels to turn together to result in progressive forward motion rather than spin independently.

Although the cerebral cortex is important in people for generating gait, it is not very important in animals. Instead, gait initiation comes from the brainstem. The clinical importance of this is that cerebrocortical disease will not generally cause overt gait abnormalities but diseases of the brainstem will. Specifically, they will cause obvious signs of weakness or loss of gait generating ability.

Additionally, if you study the tracts of the central nervous system, you will see that the cerebellum and vestibular system are responsible for coordinating sensory input. Inability to coordinate sensory input leads to ataxia. In addition to brainstem disease causing weakness, it may also cause ataxia. The quality of ataxia will depend on which coordinating centers are involved. If the cerebellum is diseased, cerebellar gait will result. If the vestibular system is involved, ataxia will have a vestibular quality. If neither cerebellum nor vestibular system is involved, proprioceptive ataxia results.

Mentation

The ascending reticular activating system is a collection of neurons that project sensory input from cranial nerves and spinal nerves (via spinal somatosensory tracts) to the cerebral cortex to arouse or awaken the individual. Alterations in arousal result when this system is damaged directly or if affected by systemic disease.

Localizing postures

Severe damage to parts of the brain can result in abnormal head and body positions. Recumbency with opisthotonus and extension of all four limbs results from physical or functional separate of the cerebral cortex. This is a decerebrate posture and mentation is usually markedly affected. Recumbency with opisthotonus and/or pleurothotonus (head turned left/right) and alternating extension/flexion of the pelvic limbs is consistent with a decerebellate posture. Mentation may be less affected.

Testing cranial nerves

Tests of cranial nerves are discussed. Remember however that we assess cranial nerves by assessing reflex arcs, which have an afferent and efferent contribution, usually from different cranial nerves. Thus an abnormal test is not specific for a cranial nerve. You must use the collective finding of multiple tests to determine which nerve is affected and where.

CN I Olfactory nerve

The only cranial nerve that doesn't get routed through the thalamus before projecting to the cerebral cortex. Not often examined except in working dogs. It is important not to use a noxious stimulus when testing olfaction. It is generally best to hide a strong-smelling treat (tuna fish, cat food, bacon) under a cup and see if the patient can find it. This is an insensitive test if the lesion is unilateral.

CN II Optic nerve

The optic nerve is a sensory nerve relaying light and visual input. Tests of optic nerve function include observation of anisocoria, changes in direct pupillary light reflex (PLR), and presence of a dazzle reflex. The efferent part of the PLR is from CN III. The efferent arc of the dazzle is CN VII.

The visual pathway separates from the PLR pathway at the level of the thalamus. The menace response utilizes CN II and the efferent part of this pathway is usually CN VII (blinking). Some animals may jerk their head away which is more of a cortical or conscious response to visual stimuli. Additionally, if CN VII is injured and an animal cannot blink, they may retract the globe in response. This is mediated by CN VI. Tracking of cotton balls and ability to navigate obstacle courses are also tests of vision. These may be more reliable tests in cats, who notoriously like to inhibit their menace response in the clinic.

CN III Oculomotor nerve

This is a motor nerve that has a somatic part that moves the eye medially (medial rectus mm.) and a parasympathetic part that causes pupillary constriction (ciliary mm). There is also a small branch that innervates the levator palpebrae mm and contributes to eyelid closure, though not as much as CN VII.

Tests of the parasympathetic part of CN III include observation of anisocoria in conjunction with direct and indirect PLR assessment. Tests of the somatic part includes observation of lateral strabismus as well as the oculocephalic reflex. The afferent part of this reflex is from the vestibular nerve. You may see very subtle ptosis associated with CN III deficits.

CN IV Trochlear nerve

This is a motor nerve that innervates the dorsal rectus muscle of the eye and causes inward rotation of the eye. Deficits of this nerve are difficult to recognize in animals with round pupils. In cats, extorsion of the eye would indicate a deficit.

CN V Trigeminal nerve

This nerve has three branches the mandibular branch, the maxillary branch, and the ophthalmic branch. The mandibular branch is predominantly motor and innervates the muscles of mastication. Deficits are recognized by testing jaw tone, observation of dropped jaw or inability to full close the mouth, and atrophy of the muscle of mastication. The maxillary branch is a sensory branch and relays sensation of touch from the skin and muscles of the face. The palpebral reflex tests maxillary innervation. The efferent response, closure of the eye, is from CN VII. The ophthalmic branch is a sensory branch that innervates the cornea and the corneal reflex can assess its integrity.

CN VI

This is a motor nerve that innervates the lateral rectus muscle of the eye to move the globe laterally and innervates the retractor bulbi to pull the globe back into the orbit.

Observation of medial strabismus indicates a deficit of VI to the affected eye. Decreased lateral movement of the eye during the oculocephalic reflex is another way to evaluate the abducens nerve. Lastly, the corneal reflex which utilizes sensory input from the cornea via CN V, ophthalmic branch, is another test of CN VI. If testing the corneal reflex it is important to use a cotton swab moistened with saline and to use very gentle pressure to avoid iatrogenic trauma.

CN VII Facial nerve

This is a sensory and motor nerve that innervates the muscle of facial expression and the inner pinnae of the ear. CN VII is the efferent part of the palpebral reflex arc. CN VII can also be assessed by the faciofacial reflex where you stimulate the inner pinnae of the ear (innervated by sensory of CN VII) and look for twitching of the ear (innervated by motor of CN VII). The facial nerve is also responsible for lacrimation (parasympathetic response). The cranial 1/3 of the taste buds of the tongue are innervated by CN VII for taste sensation. This is not evaluated in veterinary medicine.

CN VIII Vestibulocochlear nerve

Another proceedings is dedicated to further discussion of CN VIII and the vestibular system. The vestibular nerve is a special sensory nerve providing sensory input about head position and balance. Deficits can lead to positional ventrolateral strabismus, changes in the oculocephalic reflex, head tilt, and nystagmus. A complete loss of the oculocephalic reflex generally does not occur unless there is bilateral vestibular dysfunction or changes in intracranial pressure. This is due to the degree of crossover of the pathway.

Cochlear function or hearing can be assessed by creating a loud noise and observing for a conscious reaction. BAER testing is a more sensitive and specific test of the cochlear nerve.

CN IX Glossopharyngeal nerve

CN X Vagus nerve

It is difficult to assess CN IX and X separately as they are both involved in the gag reflex. CN IX is the sensory or afferent part of the reflex and CN X is the motor or efferent part. I do not test the gag reflex of aggressive animals or ones that are likely to bite me. It is important to actually try and feel constriction of the pharyngeal muscles and not simply observe swallowing. Reports of dysphagia from home are also suggestive of deficits in IX and/or X. Additionally CN IX innervates the taste buds of the caudal 2/3 of the tongue. This is not evaluated in veterinary medicine. The vagus nerve distributes branches to innervate the thoracic and abdominal viscera. This is not generally assessed on the neurologic exam though vagal nerve damage has been reported to be associated with gastric ulcers.

CN XI Spinal accessory nerve

This nerve is a motor nerve that innervates the sternocleidomastoid (part of the cervical musculature) and the trapezius muscles, which move the scapula and support the caudal neck. Presence of atrophy or shoulder weakness indicates a deficit in this nerve.

CN XII Hypoglossal nerve

This nerve provides motor innervation to the tongue. Tongue atrophy can be difficult to recognize in awake animals but you can observe for symmetrical licking of the sides of the face (peanut butter can help perform this test) or difficult in prehension of water.

Forebrain signs

As mentioned, gait is typically normal with forebrain lesions. Some animals may develop a pacing gait or circle widely. They are able to walk in a straight line, but if placed in confined area they may circle toward the side of the lesion. Weakness is not usually apparent during gait analysis but when testing postural reactions, may be decreased to absent contralateral to the lesion. The visual pathway projects visual input to the contralateral visual cortex in the occipital lobe of the cerebral cortex. This may result in visual deficits contralateral to the lesion with a normal pupillary light reflex. Vision can be assessed by the menace response, cotton ball tracking, obstacle courses, or visual placing.

Seizures are *always* a result of forebrain dysfunction whether its primary (idiopathic epilepsy) or secondary (brain tumor, inflammatory disease, metabolic disease). Structural diseases such as neoplasms, malformation, and granulomatous disease will lead to lateralizing abnormalities on the neurologic exam referable to one side of the forebrain or the other. Animals with metabolic disease as a cause of seizures may have neurologic signs consistent with forebrain dysfunction, but their signs are usually bilateral and symmetrical.

Cerebellar signs

Cerebellar disease is relatively easy to recognize on gait analysis. Animals with a cerebellar gait have spastic dysmetria (high stepping) and titubation (swaying of the trunk). They may have an intention tremor when trying to eat, drink or investigate their environment. They typically are not weak. Remember, there are no “gait generators” in the cerebellum.

There are projections from the vestibular nuclei to the cerebellum and involvement of these tracts can lead to vestibular signs such as a head tilt and nystagmus. Because of the inhibitory input of the cerebellum, the head tilt is paradoxical and is *away* from the side of the lesion.

The menace response can also be affected with cerebellar lesions, ipsilateral to the problem. Vision and PLR pathways are normal. These animals may have a decreased menace but normal tracking response and no deficit navigating an obstacle course. Similarly, cerebellar lesions may cause an enlarged palpebral fissure ipsilateral to the lesion. Palpebral reflexes, pathways that do not pass through the cerebellum, are intact.

Elevated intracranial pressure

The cranial vault has a limited ability to adapt to increases in pressure of its contents. As pressure within the calvarium rises as a result of tumor growth, inflammation, edema, hemorrhage, etc. the brain swells and starts to herniate out of the skull. Neurologic signs of brain herniation include abnormal mentation, anisocoria, slow/absent PLR, and weak oculocephalic reflex. As the pressure rises it compromises cerebral perfusion (reduced oxygen and glucose delivery). In effort to stave off impending brain death, there is a sympathetic discharge released from the brain. This release of hormones leads to an increase in blood pressure to try and restore perfusion to the brain. The heart responds to this hypertension with reflex bradycardia. This reflex is known as the Cushing’s reflex and is an imminent sign of death. Treatment should be directed toward reduction of intracranial pressure NOT at restoring normal heart rate. Patients with elevated intracranial pressure may also demonstrate ataxic breathing, hypo or hyperventilation, and various arrhythmias (brain-heart syndrome).

Suggested reading

De Lahunta and Glass. Veterinary Neuroanatomy and Clinical Neurology, 4th edition.

Neurolocalization of Spinal Cord Disease

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A lower motor neuron (LMN) is any nerve that innervates a muscle group. The important (most noticeable) lower motor neurons are the ones that supply the legs. The LMN is part of the motor unit. The rest of the motor unit consists of the neuromuscular junction, the muscle fibers, the muscle spindle and sensory nerve. Each motor unit forms a loop going through the spinal cord. Some motor units involve interneurons within the spinal cord. The motor unit has to be intact for an animal to have a reflex. Remember that each segment of the spine will have lower motor neurons. It's just that the ones at T10 don't do very much (innervate skin and epaxial musculature in a small area) where as the ones at the intumescence do a lot (innervate the legs).

An upper motor neuron is any neuron that "supervises" another neuron. If you injure an upper motor neuron, that supervision goes away and there's "chaos" distal to the injury. This chaos manifests itself as increased reflexes (you percuss the tendon once and the leg kicks out 4 times) and spasticity. Upper motor neurons are generational. The "grandmother" of all UMN is the cerebellum. The cerebellum supervises the cortical and the brainstem neurons. The cortical neurons supervise the brainstem neurons. The brain stem neurons give rise to the motor neurons that travel down the spinal cord motor tracts. The neurons of the motor tracts (UMN) supervise the alpha motor neurons (LMN) of the motor unit.

Gait analysis is critically important to neurolocalization and often you can localize a spinal cord lesion on gait alone. There are 2 qualities we evaluate in gait analysis: ataxia and weakness.

Ataxia is by definition the inability to coordinate voluntary muscle activity. There are three kinds of ataxia: vestibular, cerebellar, and proprioceptive. The vestibular system and cerebellum are both major gait coordinators; if they are damaged, incoordination results. In order to coordinate the walking function, sensory information about limb position has to be integrated. This sensory information is known as proprioception. The spinal cord contains all the sensory projections from the body and limbs, if it's injured this information won't be able to be integrated. Proprioceptive ataxia results. Proprioceptive ataxia is simply failure to have limb position integrated into the gait. Animals with proprioceptive ataxia will cross their legs over, take too high steps (hypermetria, usually over-reaching/floating quality), or otherwise look "drunk." The lower motor neuron has to be intact for ataxia to happen. If the LMN can't fire, you can't walk; if you can't walk, you can't look ataxic. Thus proprioceptive ataxia is an UMN sign. Remember that sensory axons are usually heavily myelinated and most susceptible to compression. This is why ataxia is the first sign of compressive spinal cord injury.

Weakness simply means lacking strength. When watching an animal walk, weakness will manifest as difficulty rising, shortened stride (hypometria), dropped carpi/tarsi, dragging/scuffing, and falling down. If the generator (brainstem) fails, you are weak. If the motor connectors (spinal cord) fail, you are weak. If the effectors (motor unit) fail, you are weak. Thus weakness can be associated with UMN or LMN disease. The rest of the neuro exam (ataxia, reflexes, limb tone) will help you determine which one (UMN or LMN) is causing the weakness.

Testing postural reactions is done to see if an animal knows where its limbs are in space. It is a test of position sense. However, postural reaction deficits are not by themselves localizing. For example, if an animal fails the test for conscious proprioception (position sense) in one leg, the lesion could be anywhere in the pathway for proprioception from the peripheral nerve to the brain. There are two proprioception pathways that we test with postural reactions: Conscious Proprioception and Unconscious Proprioception.

Conscious proprioception is tested by placing the paw upside down and seeing if the animal corrects it. The pathway begins with the sensory receptors on the dorsal surface of the paw. Sensory information would then travel up the sensory nerve, through the sensory ganglion (dorsal root ganglion), up the spinal cord sensory tracts, integrated in the cerebral **cortex** and motor centers (brainstem), back down through the motor tracts of the spinal cord to the motor nerve, to the muscle to return the leg to a normal position. Because this pathway is integrated in the cerebral cortex, the "thinking part" of the brain, it is considered conscious. Consciousness is awareness of what happens.

Unconscious proprioception is tested by shifting an animal's weight away from its center of gravity and seeing if they "catch" themselves and re-center. This is tested by hopping and hemiwalking. The pathway is very similar to that described above except that the sensory input is integrated in the **cerebellum**, a part of the brain that doesn't involve conscious awareness.

Postural reaction deficits occur with a lesion anywhere in that pathway and thus could be a result of upper motor neuron or lower motor neuron injury.

Reflexes are a specific evaluation of the motor unit. If a part of the motor unit is damaged, reflexes are decreased or absent. There may also be loss of tone to the limb (in the forelimbs this is more reliable of UMN or LMN change than reflexes). With spinal cord injury, depressed reflexes result from injury to the part of the cord that contains the alpha motor neurons of the limbs: the cervical (C6-

T2) and lumbar (L4-S3) intumescences. If injury occurs above the intumescence, upper motor neuron signs result (C1-5 and T3-L3 lesions).

Reflexes of the thoracic limb

Reflex	Peripheral Nerve and Spinal Cord Segments Assessed	Initiating Stimulus	Efferent Response
Biceps	Musculocutaneous nerve; C6-C8 segments	Percuss biceps tendon	Flexion of elbow
Triceps	Radial nerve; C7-T1 segments	Percuss triceps tendon	Extension of elbow
Extensor Carpi Radialis	Radial nerve; C7-T1 segments	Percuss belly of extensor carpi radialis muscle	Extension of carpus
Flexor/Withdrawal	Musculocutaneous, axillary, radial, median, and ulnar nerves; C6-T2 segments	Pinch digit	Flexion of shoulder, elbow, and carpus

The withdrawal reflex or flexor reflex is the most reliable reflex in the thoracic limb. The others can be difficult to elicit and are not always accurate for lesion localization. It is also important to assess tone of the limb, and this may be a more reliable indicator of UMN (increased tone) vs LMN (decreased tone) change.

Reflexes of the pelvic limb

Reflex	Peripheral Nerve and Spinal Cord Segments Assessed	Initiating Stimulus	Efferent Response
Sciatic	Sciatic nerve; L7-S1 segments	Percuss finger resting in the sciatic notch	Extension of limb
Patellar	Femoral nerve; L4-6 segments	Percuss patellar tendon	Extension of stifle
Cranial tibial	Sciatic nerve, peroneal branch; L6-S1 segments	Percuss belly of cranial tibial muscle	Flexion of hock
Gastrocnemius	Sciatic nerve, tibial branch; L6-S1 segments	Percuss gastrocnemius tendon	Extension of hock
Flexor/Withdrawal	Femoral and Sciatic nerves; L4-S1	Pinch digit	Flexion of hip, stifle, and hock
Perineal	Perineal nerve; S1-3	Pinch perianal tissue	Constriction of anus

The patellar and withdrawal/flexor reflexes are the most reliable in the pelvic limb. The pudendal nerve is responsible for innervation to the perineum and so the **perineal reflex** and anal tone is a reflection of pudendal nerve (S1-3) integrity.

With chronic UMN injury the neurons may reorganize as they try to heal. As a result, abnormal reflexes (mass reflexes) may develop. We don't know exactly how long an injury has to persist for these to develop but it may be as few as 2 weeks. A crossed extensor reflex is a mass reflex that occurs when you pinch the toes of one leg and as that leg withdraws, the other one is extended. This reflex is normal if you are walking around (so you don't fall over when you pick up one leg), but should be inhibited when in lateral recumbency. A Babinski reflex is an abnormal extension of the digits when you stroke the bottom of the foot from toe to heel/hock.

Micturition, once initiated, behaves like a reflex. Thus urinary continence is evaluated similar to reflexes. If the nerves to the detrusor (pelvic n, S1-2 segments) and sphincter (pudendal n, S2-3 segments) are damaged, a LMN bladder develops. A LMN bladder lacks tone and is easy to express (no sphincter control). An UMN bladder has excess tone and is difficult to express (tight sphincter). Cortical control over urinary function is lost near the same time that motor function is lost because those tracts are similarly myelinated.

Spinal pain results from damage to nociceptors. Nociceptors are located in the meninges, periosteum, annulus of the disc, joint capsule of the spinal articular facets, ligaments, and nerve roots. Pain may also result from damage within the dorsal horn due to alterations in neurotransmitters involved in pain perception such as substance P. Focal pain can be a localizing sign.

There are two neurologic causes of muscle atrophy: denervation and disuse. Denervation atrophy results from LMN injury. If the nerve is unable to make a normal connection with the muscle, the muscle innervated will atrophy very quickly (days). Disuse atrophy is much like the atrophy that occurs if we don't go work out regularly at the gym. It is much less pronounced than denervation atrophy and happens more gradually, usually over weeks to months.

The most resilient nociceptive fibers are those located deep in the white matter and the grey/white matter junction. These fibers only become damaged with the most severe types of injury. When damaged, there is complete analgesia caudal to the injured segment.

Reflexes may still be intact but there will be no conscious recognition of painful stimuli distal to the injured site. THIS IS A CRITICAL DISTINCTION: withdrawal ≠ sensation. Presence or absence of deep pain is of utmost importance in determining long term prognosis associated with spinal cord injury.

Segmental signs

C1-5 Myelopathy: UMN x4

- Gait: Ataxic in all 4 limbs due to UMN injury. The quality of ataxia is an over-reaching/floating type hypermetria. Weakness may develop with more severe injury.
- Postural reactions: Affected in all 4 limbs in both paw placement and hopping
- Reflexes/tone: Normal to increased in all 4 limbs
- Atrophy: disuse or none
- Other: Severe injury at C1-2 or the spinomedullary junction may result in opisthotonus.

C6-T2 Myelopathy: LMN FL, UMN RL

- Gait: Short-strided and predominantly weak in the forelimbs and ataxic in the pelvic limbs. Pelvic limb weakness may also be present with more severe injury. The weakness in the forelimbs is a result of involvement of the cervical intumescence and thus the lower motor neurons of the front legs. UMN signs develop in the pelvic limbs due to involvement of the cervical white matter tracts.
- Postural reactions: affected in all 4 limbs in both paw placement and hopping.
- Reflexes/tone: decreased tone and weak reflexes in the front limbs. Normal to increased reflexes and tone in the pelvic limbs.
- Atrophy: Denervation type atrophy may be present in the front limbs. Disuse or no atrophy in pelvic limbs.
- Other: The sympathetic nerves, which originated up in the brain, exit the spinal cord at T1-2 to form the sympathetic trunk. Thus an injury involving the T1-2 spinal segments or nerve roots may cause ipsilateral Horner's syndrome. The lateral thoracic nerve originates at T1-2. This nerve is responsible for the efferent branch of the panniculus reflex. If damaged there will be an ipsilateral loss of panniculus no matter where you put the stimulus (pinch). The phrenic nerve, which innervates the diaphragm, originates in the C5-7 segments. If injured, diaphragmatic weakness may occur and a patient will have poor chest excursions because s/he cannot move the diaphragm to breathe.

T3-L3 Myelopathy: Normal FL, UMN RL

- Gait: normal thoracic limbs, ataxic in pelvic limbs. Weakness develops with more severe injury.
- Postural reactions: affected in pelvic limbs only, hopping and paw placement
- Reflexes/tone: normal in the thoracic limbs, normal to increased in the pelvic limbs.
- Atrophy: disuse in the pelvic limbs or none.
- Other: Animals with severe T3-L3 injury may develop Schiff-Sherington posture. This posture is characterized by stiff appearing neck and forelimb. However, when you test the function and reflexes of the front legs they are normal. This is <u>not</u> prognostic! It <u>is</u> localizing since ONLY T3-L3 injury causes Schiff-Sherington posture.

L4-S3 Myelopathy: Normal FL, LMN RL

- Gait: Normal thoracic limbs, weakness in pelvic limbs. A plantigrade stance indicates inability to extend the hock and thus is specific for sciatic nerve injury (L6-S1). Inability to stand or advance the limb is specific for femoral nerve injury (L4-6). Flaccid tail (S1-3 +/- caudal)
- Postural reactions: affected in pelvic limbs only
- Reflexes/tone: normal in the thoracic limbs, decreased in the pelvic limbs, +/- decreased anal tone (S1-3)
- Atrophy: denervation atrophy in the pelvic limbs

Suggested reading

De Lahunta and Glass. Veterinary Neuroanatomy and Clinical Neurology, 4th edition.

New Anti-Epileptic Medications: When and How to Use Them

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Seizures are always an indication of forebrain dysfunction. That dysfunction may be a primary functional change (primary or idiopathic epilepsy) or due a secondary cause. Secondary epilepsy is either a result of structural disease (brain tumor, inflammatory disease) or a normal brain reacting to systemic abnormalities (metabolic brain dysfunction, hypoglycemia, toxicity). Always treat the underlying cause of the seizures in addition to managing the epilepsy with anti-convulsant medications. For primary epilepsy, it is extremely important to have an open discussion with the owners at the onset of the seizure disorder about long term management and expectations. Complete seizure elimination is often unrealistic. Managing epileptics requires significant emotional, time, and monetary investments.

Indications for maintenance anticonvulsant therapy

- 3 or more seizures in $\leq$ 6 weeks *this is VT criteria
- Cluster seizures
- Status epilepticus or a seizure $\geq$ 2 minutes
- Intracranial etiology + seizures

A single seizure in a dog (not necessarily a cat) that is physically, biochemically, and neurologically normal may not need to be pharmaceutically treated. No one knows for any one patient when a seizure or seizures may turn into a life threatening event so repeat seizures are cause for concern. Although not proven to occur, kindling phenomenon may play a role in worsening a seizure disorder. Kindling occurs in the experimental setting where frequent repeated stimulation of cerebral neurons set up circuitry that initiates spontaneous seizures. With the exception of status epilepticus, seizures are generally not life threatening. They can significantly impact quality of life and severe phenotypes may ultimately shorten an animal's longevity. Sudden unexpected death in epilepsy patients (SUDEP) occurs in about 1/1,000 human epilepsy patients. Risk factors include frequent, generalized seizure activity, poor pharmacologic compliance, and increased number of anti-epileptic drugs (AED) used (SUDEP Awareness 2010).

First line AED

There are numerous options available for pharmacologic treatment of seizures. The traditional anti-epileptic drugs (AED) include phenobarbital, potassium bromide (dogs only), and diazepam (cats only). The advantages of traditional AED are that they are known to be effective, they are inexpensive, and monitoring parameters and side effects are well described. The disadvantage of most traditional AEDs is the high incidence of side effects, primarily polydipsia, polyuria, and polyphagia. More contemporary AEDs include zonisamide and levetiracetam. Some consider these only as secondary or tertiary drugs, but more veterinarians and veterinary neurologists are using them as first line AEDs. The advantage they offer is the apparent lack of side effects. Generics are available so these drugs are more affordable than they used to be but can still be expensive in large patients. Because they are relatively new, we are still learning how effective they are as primary AED, the extent/appropriateness of monitoring, and spectrum of side effects.

Secondary and tertiary AED

Any of the above mentioned medications can be added as secondary or tertiary therapy when monotherapy fails. Approximately 80% of dogs respond to a traditional monotherapy protocol (phenobarbital or potassium bromide). Another 80% respond to combined therapy. The remaining dogs are considered refractory epileptics and require 3 or more AED for adequate seizure control. These are the animals which often experience decrease longevity. Euthanasia may be pursued for quality of life purposes but some animals succumb to the seizures themselves or complications of seizure therapy.

A second AED may be added when seizure control is still poor AND the primary AED is at the upper limit of the therapeutic range. The same rule applies to adding a tertiary medication. It is extremely important to have current serum concentrations of drugs prior to adjusting the dose. The current serum concentration will also guide your dose adjustment.

It is unknown in veterinary medicine if a drug with a particular MOA is better for a patient with a certain seizure phenotype, or if it is ultimately the combination of MOA of multiple drugs that is beneficial. If the first drug has any demonstrable efficacy, I do not discontinue it when I start the secondary AED. I might consider weaning drug #1 if the patient is seizure free for an extended period (1 year) or if side effects are a problem. I will not wean medication #1 until medication #2 is at steady state.

We also don't know a lot about the efficacy of pulsed therapy for cluster seizures. It would be interesting to know if a patient with cluster seizures would be better managed on 2 AED daily or one AED daily with the second administered only near the time of clusters. This is certainly more affordable for the client but might not be in the best interest of the patient.

Alternative therapies

Ketogenic diets are useful in children but are ineffective in dogs. Hypoallergenic diets and acupuncture have been touted as having anti-convulsant properties but these remain unproven. They are unlikely to hurt the animal but have no known efficacy. Vagal stimulation can be provided by an implantable stimulator, ocular pressure, or carotid pressure. A new external device is undergoing clinical evaluation. Vagal stimulation via ocular or carotid pressure may be useful in emergent situations when IV access is difficult to obtain. Implantable devices have been used in refractory idiopathic epileptics with some success. Currently the implantable device is cost-prohibitive.

Epilepsy surgery

Surgical treatment for epilepsy is pursued in children but is infrequently performed in the veterinary population. One surgical option is cortical resection of the seizure focus. An EEG is necessary to identify the seizure electrical origin and in people the ideal way to do this is with subdurally inserted electrodes. A corpus callosotomy, division of the white matter of the corpus callosum between the two cerebral hemispheres, may prevent seizure generalization. Partial/focal seizures may still occur. Lastly, in a certain population of children, unilateral hemispherectomies have been described. Because of neuroplasticity in the young, they tolerate the procedure relatively well. Ben Carson was the innovator of this procedure and his story is capitulated in *Gifted Hands*.

Although neoplasms of the brain contribute to secondary seizure disorders, removal of the tumor does not equate to removal of the seizure focus. In fact, much of the time it is the peri-tumoral neural tissue that is responsible for the seizure and not the tumor per se. This tissue is identified by subdural EEG and can be resected (for example, children with tuberous sclerosis).

Goal

The primary goal of beginning AED is to reduce seizure frequency. A medication is considered effective if the seizure frequency is reduced by 50% (e.g. 6 seizures/month to 3 seizures/month). Even though a medication is considered effective, it may not be enough to achieve what is considered good seizure control (no seizures or infrequent seizures, for example <3 seizures/6 weeks). Secondary goals include reduction in the duration of the seizure or decrease in severity of the seizure phenotype. Ideally we would like to minimize cost for the owner and side effects in the patient.

Assessment

Although subjective input from the owner determines if the seizure phenotype or duration has changed, we try to rely on objective data about the seizure frequency to effectively assess the AED. It is extremely valuable for the owner to maintain a seizure log, recording when a seizure occurs, triggers, duration, and appearance. A reduction in seizure frequency by 50% or more is considered excellent anti-convulsant therapy. A reduction of 25-50% is good, $\leq$ 25% fair, and no change is poor or ineffective.

As long as a drug has some efficacy, it should not be discontinued. If seizure control is still poor, the current AED can be increased. If at a therapeutic maximum, additional AED should be given IN CONJUNCTION with the primary AED.

Monitoring

Monitoring is dependent on the medication used since pharmacokinetics differ. In general after beginning an AED, serum concentration should be evaluated at steady state (5-7 half-lives) and then every 6 months. Since there are no established therapeutic ranges for the newer AED, monitoring is considered optional by some. I recommend monitoring with the new AEDs as the information for the individual is meaningful, even if the therapeutic range provided is not. Phenobarbital is unique in that it causes hepatic induction of the cytochrome P450 enzymes. This occurs about 2-3 months into therapy. Since phenobarbital is primarily metabolized by this enzyme system, further enzymatic induction leads to increased metabolism of the drug and a subsequent drop in the steady state concentration. Thus with phenobarbital, serum concentrations should be evaluated at steady state, three months, six months, and then every six months. Because of this enzymatic induction, phenobarbital administration may also alter metabolism of other medications and endogenous hormones. For this reason, animals on phenobarbital may have low thyroid values and require higher dosages of hepatically metabolized medications. It can be extremely difficult to prove if an animal on phenobarbital has concurrent hypothyroidism. Generally if they are exhibiting clinical signs of hypothyroidism, treatment is indicated.

Any time a patient has a breakthrough in seizure control, serum drug concentrations should be evaluated to see if that is the cause of the breakthrough and to make appropriate dose adjustments, if needed. Every time you adjust a dose, you are changing the steady state and will need to re-evaluate serum concentrations accordingly. Failing to appropriately monitor patients is the most common cause of seizure therapy failure.

Changes in other organ function can affect the metabolism of AED and should be evaluated every 6 months or annually in seizure patients. Ideally a CBC, serum biochemistry profile, and urinalysis are done in addition to serum concentrations. At a minimum renal values, liver values and urine specific gravity should be performed. Unlike other drugs, long term phenobarbital therapy may actually cause hepatopathy and some recommend a fasting bile acid test in addition to minimum database every 6-12 months. For animals on zonisamide or felbamate, Schirmer tear tests should be performed at 2 weeks, 2 months, and then every 6 months as KCS may occur. Chronic use of sulfa drugs like zonisamide may also alter thyroid function and this should be evaluated annually or in animals exhibiting clinical signs consistent with hypothyroidism.

Weaning medications

AEDs should never be stopped abruptly due to the possibility of inducing a seizure from withdrawal effects. I typically try to wean phenobarbital before bromide in a patient receiving both those medications. My philosophy is that phenobarbital is associated with potentially more life-threatening adverse effects (hepatotoxicity, hepatocutaneous syndrome, bone marrow suppression) than bromide, especially when maintained at chronically high normal serum concentrations. I never recommend weaning a dog with symptomatic epilepsy from their AED unless they develop a life threatening complication associated with it.

Some idiopathic epileptics can eventually be weaned off medication. I only consider doing this in patients who responded well to monotherapy or possibly dual-therapy AND who've been seizure FREE for at least a year. I wean by decreasing the dose 25% every 3-4 weeks. If seizures recur during the weaning, I go back to the last effective dose, recheck the serum concentration and wait twice as long (2 years) before attempting weaning again. If two drugs are being used, I wean one at a time. I am extremely reluctant to wean dogs who were previously refractory, even if they have been seizure free for long periods of time.

Summary of AED

Drug Name	Species	Advantages	Starting Dose	Therapeutic Range	Adverse Effects
Phenobarbital/Primidone	C, F	Known efficacy, IV formulation, neuroprotective	2-4 mg/kg PO q12h	15-45 ug/ml	PU, PD, PP, ataxia, sedation
KBr/NaBr	C	Known efficacy	20-40 mg/kg PO q24h	1-3 mg/ml	PU, PD, PP, ataxia, sedation, GI upset, aggression
Diazepam	F	No monitoring, appetite stimulant	2-10 mg/kg PO q8-12h		Sedation, hepatic necrosis
Zonisamide	C, F	Safe, objective efficacy, BID dosing	5-10 mg/kg PO q12h (q24 in cats)	10-50 ug/ml	Sedation, ataxia, GI upset, KCS, rare idiosyncratic rxn
Levetiracetam	C,F	Safe, few side effects	20 mg/kg PO q8h (q12h in cats)		
Chlorazepate	C, (F)	Cluster seizure pulse therapy	0.5-2 mg/kg PO q8h	100-400 ng/ml	Sedation, ataxia, cost
Felbamate	C	Non-sedating, no monitoring	15 mg/kg PO q8h	20-100 ug/ml	Hepatotoxicity, myelosuppression, tremors
Gabapentin	C, F	Safe, no monitoring, therapeutic for other neurologic diseases	10-20 mg/kg PO q6-8h	4-16 mg/L	Sedation ,tremors, limited efficacy
Pregabalin	C, F	Same as gabapentin	3-4 mg/kg PO q8-12h		Expensive, limited efficacy
Topiramate	C	Safe, no monitoring, partial seizures	2-10 mg/kg PO q12h (C); 12-25 mg/cat q8-12h (F)		Lethargy, GI upset, ataxia, teratogenic

C = canine, F = feline

Summary of MOA

Drug	Na+ Channel Modulation	GABA Facilitation	Ca++ Channel Modulation	Reduction in Excitatory Neurotransmission
Barbiturates		++	+	+
Benzodiazepines		++		
Bromide		++		
Felbamate	+	++	+	+
Gabapentin/Pregabalin	+	++ (indirect)	++	+
Zonisamide	+		++	
Levetiracetam		++(indirect)		
Topiramate	+		+	+

Summary of monitoring

Test	Phenobarbital and Primidone	KBr	Diazepam	Levetiracetam	Zonisamide	Gabapentin and Pregabalin
Serum concentration	X ss, 3m, 6m, q6m	X ss, q6m		X ss, q6m	X ss, q6m	
CBC	X					
Chemistry	X	X	X	X	X	X
Bile Acid Profile	X		+/-		+/-	
Urinalysis	X	X		X	X	X

Suggested reading

Dewey C. A Practical Guide to Canine and Feline Neurology. Chapters 5 and 7. Second ed. 2008.

Rehabilitation for Neurologic Patients

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There is a wealth of knowledge regarding the importance and utilization of physical therapy in human medicine. Unfortunately, similar studies have yet to be under taken in veterinary medicine. The literature that is available primarily applies rehabilitation techniques to canine patients with cranial cruciate ligamentous injury. A single study examining the impact of a specific rehabilitation program on survival of dogs with degenerative myelopathy showed significant benefit (Kathmann et al 2006). Additional research looking at the impact of physical rehabilitation on neurologic and orthopedic conditions is lacking in veterinary medicine.

Physical rehabilitation may promote faster recovery following surgery or in non-surgical patients by improving blood flow, limiting inflammation, maintaining and increasing muscle mass, promoting joint health, increasing range of motion, improving quality of movement, assisting weight loss, and preventing complications. A wide variety of techniques and modalities are used to achieve these beneficial effects. The patient's demeanor, diagnosis, and prognosis as well as the commitment and financial limitations of the owner will dictate what activities and instrumentation may be used.

Physical rehabilitation has known therapeutic effects but is also a psychologically rewarding engagement for many clients and patients. It allows and encourages client-patient interaction and prevents boredom during periods of rest and healing. That being said, not every neurologic disease will benefit from all rehabilitation techniques and in some cases there are known contra-indications for particular therapies. Thus having a diagnosis before initiating therapy is very important.

Making a proper diagnosis does not necessarily mean all cases must have advanced diagnostic imaging, though it is ideal. A thorough history, physical exam, neurologic exam, and radiographic evaluation may be sufficient in some cases. Radiographs are frequently not diagnostic for most conditions for which physical rehabilitation is indicated, e.g. degenerative myelopathy, intervertebral disc disease, degenerative lumbosacral stenosis, fibrocartilaginous embolism, cervical spondylomyelopathy. However, they can help rule out diseases that would require a radically different therapeutic approach, e.g. diskospondylitis, osseous neoplasia, atlanto-axial luxation.

For non-surgical conditions such as degenerative myelopathy and fibrocartilaginous embolism, more is better. Physical rehabilitation exercises should be done early and often. For post-operative patients only gentle exercises that do not involve walking should be done in the first 2 weeks (weight shifting, stretching, etc). More active exercises can be added gradually after that. For dogs with suspected type I intervertebral disc herniations, strict rest must be adhered to for 2 weeks. This is critical to allow any tears in the annulus to heal so that additional disc material does not herniate. If the patient is improving, gentle and passive exercises can be initiated after 2 weeks. After 1 month, additional active exercises can be added.

Once a diagnosis has been made, talk with the clients about their monetary and time investment as well as their expectations. It would be unrealistic for clients with a 7 year old, grade 5 paraplegic greyhound to expect their dog to return to racing and not need long term medical care.

Assessing patients for rehabilitation involves not only the neuroanatomic localization of a problem, but an assessment of their neuromuscular function. What specific weaknesses are present? How severe are they? Is there a balance problem? How uncomfortable is the patient? What asymmetries are there? How is the animal trying to adapt to accommodate these deficiencies? Has this resulted in abnormal movement patterns? What restricted movement patterns are there? The rehabilitation practitioner's assessment at first seems much more subjective but objective measures can be taken to corroborate these findings. Simple measures such as circumferential muscle mass can be evaluated using a tension loading measuring tape. Joint range of motion can be quantified using goniometry as well as characterizing the end feel (soft, hard, empty); this is typically less important than assessment of muscle mass for neurologic patients unless comorbid conditions are at play. More expensive equipment such as stance analyzers, kinematic motion sensors, and force plates are also available at some institutions/practices.

Pain control is essential. Uncomfortable patients are not going to want to participate in activities and will be limited by the severity of their pain. Pharmaceutical control should always be initiated first and to whatever extent possible. Acupuncture and alternative/complementary medicine can be considered as well. Once a patient is comfortable enough to willingly engage in your plan, the therapy itself and establishment of normal movement patterns will also be pain relieving.

Ground therapy exercises are only limited by your imagination. Standard exercises have been described (Millis and Levine 2013). Some difficult patients won't always cooperate and cats are notoriously picky. Phsyio balls, BOSU (bottom side up) boards, balance boards, mattresses, treadmills, steps, ramps, and obstacle courses can all be used to achieve active work. Motivational tools are different for every patient and could include food, toys, praise, or even the opportunity to escape! Which exercise you implement just depends on what you want to achieve. For example, a patient who has caudal cervical spondylomyelopathy and associated thoracic limb weakness, particularly in the triceps, may need to work on improving extension strength. Having the patient rest in sternal recumbency and "push up" for a treat may achieve this. Simple weight bearing exercises with support offer a less dynamic alternative.

You can also utilize assistive devices to achieve proper movement patterns when walking. For example, a patient that drags his toes from a spinal cord injury but who is otherwise ambulating well may benefit from a toe-up device. This is a tension band that goes from the affected digits to a chest harness. Specialized companies manufacture such devices but you can also fashion them yourself using therapy bands and an ordinary harness. Therapy bands can also allow you to vary the support you provide when used as a dynamic sling under the chest or belly. They can be attached to a limb to provide resistance or used as hobbles to combat abduction. Prosthetics/orthotics can be fashioned if more permanent abnormalities are present (distal tibial nerve laceration). Carts, while often thought of as a permanent mobility device, can be utilized for transitioning patients to more difficult activities.

The underwater treadmill is one of the most beloved rehabilitation tools but also the most expensive. Water therapies provide buoyancy, warmth, compression, and resistance which can each be beneficial. Swimming, while also an aquatic exercise, typically uses more forelimb strength and for this reason might be useful for promoting thoracic limb active range of motion. The buoyance of water has huge advantages for neurologic patients who often have substantial weakness. Depending on water height you can "eliminate" up to 90% body weight. This requires the patient to bear only 10% of his normal weight which may make moving substantially less difficult under such a light load. For extra large patients, having the water bear the brunt of patient weight also makes it easier to perform assisted walking. This is where the practitioner is in the water with the patient and places the patient's limbs to simulate walking. Just floating large, down dogs keeps them in a more normal, upright position and the warmth and gentle movements help promote lymphatic flow. It can be a nice change of pace from lying in lateral recumbency. Patients with wound infections, urinary tract infections, or cardio-respiratory issues should not go in the underwater treadmill.

Therapeutic ultrasound is a way to heat superficial tissues. Warm tissue is more relaxed and stretchable and has improved blood flow due to vasodilation. Therapeutic ultrasound is helpful in addressing muscle trigger points or spasms as well as stretching tendons and soft tissue (contractures). It is more focused and can be applied to slightly deeper tissue than warm packs but a similar result is achieved. Therapeutic ultrasound can also be combined with electrical stimulation to relieve pain. These warming techniques are best used at the beginning of a therapy session.

Electrical stimulation can be used to contract the muscle (neuromuscular electrical stimulation or NMES) or for pain control (inferential current, pre-modulated current). TENS units (trans cutaneous electrical nerve stimulator) are portable electrical stimulation units for pain control. NMES can help improve muscle strength, reduce disuse atrophy, improve lymphatic return, and increase blood flow. Use is predominantly limited by how well the patient tolerates the degree of stimulus necessary to lead to a sustained muscle contraction. Electrical stimulation for pain control is thought to induce endorphins and "close the gate" for incoming nociceptor released neurotransmitters.

Acupuncture does not necessarily fall under the category of physical rehabilitation but plays an important role in managing some neurologic diseases. It can be useful not only for pain control but also for neural stimulation.

Low level light laser can be very useful for wound healing and patients with osteoarthritis who have marked limitations on their ability to perform activities. However, laser is not a panacea for all. Laser is stimulatory to tissue. When it comes to neoplasia, the last thing we want to do is encourage it! In older dogs with spinal cord disease, laser may not be the best choice unless you have advanced imaging to effectively rule out neoplastic causes of the clinical signs. Similarly, the genetic mutation that leads to degenerative myelopathy is a gain of function mutation. This mutation affects the SOD-1 gene, which mean it has *more* antioxidant activity than normal. In theory, if we apply laser we might worsen this. Yet another reason to be cautious of using laser along the vertebral columns of older dogs. Genetic testing for degenerative myelopathy is available through OFA (offa.org).

Suggested reading

Millis and Levine. Canine Rehabilitation and Physical Therapy, 2nd edition.