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Neurology

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PD Dr. Michael Leschnik
Austria
Email: michael.leschnik@vetmeduni.ac.at

Dr. PhD Akos Pakozdy, Dipl.ECVN
Austria
Email: akos.pakozdy@vetmeduni.ac.at

PD Dr. med. vet. (habil.) Martin Schmidt, Diplomate ECVN
Germany
Email: Martin.J.Schmidt@vetmed.uni-giessen.de
MRI in neurological disorders (Epilepsy)

PD Dr. med. vet. (habil.) Martin Schmidt

When it comes to epilepsy the role and benefit of magnetic resonance imaging (MRI) can be different. Low-field strength MRI can usually identify obvious pathology with a certain size and signal intensity that takes up contrast, such as neoplasms, large inflammatory lesions and severe malformations. One might argue that the benefit of low field MRI is limited to identification of structural substrates that can be surgically or medically treated. However, this is most relevant for practice. The diagnosis of structural changes like infarctions, hemorrhage and tumors is straightforward. Low grade astrocytomas can lack major structural changes and contrast uptake. Inflammatory lesions are also routinely diagnosed with MRI, however, we see a number of cats with the neurologic form feline infectious peritonitis (FIP) without MRI findings and even normal CSF, in which FIP is diagnosed post mortem. Ventricular enlargement in mesocephalic cats should not be assessed as normal and might be indicative for FIP. Viral infections show also often unremarkable MRIs. Toxic encephalopathies are usually purely functional and do not lead to structural changes.

Metabolic

Portosystemic shunt/hyperammonemia
Different lesions have been found in association with liver problems in dogs. Symmetrical hyperintense lesions in the cerebral cortex have been described accompanied by generalized widened sulci, consistent with brain atrophy. Hyperintense focal areas in the lentiform nuclei on T1-weighted (T1W) images, which did not enhance after intravenous gadolinium, have also been found.

Hydroxaglutaric aciduria
MRIs findings include bilaterally symmetric, diffuse regions of gray matter hyperintensity on the T2-weighted images most pronounced in the thalamus, basal ganglia, brainstem, and cerebellar nuclei. These lesions are mildly hypointense on T1-weighted scans. No contrast enhancement is seen on T1-weighted images after the IV injection of a gadolinium contrast agent.

Thiamine/Cobalamine deficiency
Bilateral, symmetric T2W hyperintensities are described in both hypovitaminoses, which are usually confined to the caudate nuclei, lateral geniculate nuclei, red nucleus, caudal colliculi, facial and vestibular nuclei. Changes are more pronounced in cobalamin deficiency.
Neuronal ceroid lipofuscinosi
This storage disease leads to diffuse severe dilation of the cerebral sulci, dilated fissures of diencephalons, midbrain, and cerebellum, and lateral ventricular enlargement, suggesting atrophy of the forebrain.

High field MRI
The advent of high-resolution MRI with a dedicated epilepsy protocol has significantly increased the frequency with which pathologic substrates for epilepsy are identified. This is important to separate primary epilepsy from other structural causes. High field MRI can assist with classification of an epileptic disease or syndrome, determine prognosis, and predict long-term intractability to antiepileptic medications. Specific standardized veterinary epilepsy-specific MRI protocol have been proposed, which may facilitate more detailed examination of areas susceptible to generating and perpetuating seizures.

Congenital cortical malformations
Malformations with simplified gyral patterns have been described in animals. These conditions result from abnormally decreased cellular proliferation. Lissencephalies and other severe malformations can easily be diagnosed. Heterotopias represent collections of normal neurons located in abnormal locations, anywhere from the subependymal region to the cerebral cortex. They result from the arrest of neuroblast migration. These subtle aberrations and other cytoarchitectural disarrays of the cortex are scarcely described in veterinary medicine. To improve the identification of heterotopias MRI scan should include T2-weighted, proton density and fluid attenuated inversion recovery (FLAIR) sequences to cover the whole brain in at least two orthogonal planes, with the minimum slice thickness possible.

Hippocampal sclerosis
Hippocampal sclerosis (HS) is the single most common pathology underlying refractory focal epilepsy in humans, and is amenable to surgical treatment. An autoimmune limbic encephalitis exists in cats, as they are thought to in humans. Bilateral hyperintensity in the hippocampus in T2W and FLAIR and contrast enhancement in T1W has been found in these cats. However, evaluation of medial temporal structures (hippocampus, amygdala, entorhinal cortex, and parahippocampal gyrus) are needed using a standardized protocol.
Future goals of MRI

The third step of diagnostic imaging is research orientated. Functional examination can help to identify a seizure focus and identify potential surgical candidates.

Quantitative MRI assessment of the brain

In clinical practice, hippocampal asymmetry may be visually apparent to neuroimaging specialists, but lesser degrees of asymmetry are hard to identify. Assessment of hippocampal atrophy may be improved by measuring hippocampal volumes. Contiguous thin slices enhances the reliability of measurements.

Longitudinal studies of the effect of epilepsy on the brain

Voxel-based morphometric methods should be applied in longitudinal studies to identify subtle changes in the brain and to determine the effects of epilepsy. It remains unclear as to whether hippocampal damage is associated with a longer duration of epilepsy and a greater number of seizures. Longitudinal studies might help to ascribe cause and effect.

Identification of a seizure focus

Focal increases in cerebral blood delivery have been identified in human patients with frequent interictal spikes. The feasibility of combining MRI data with EEGs data needs to be studied. These results may be used to evaluate animals that might be candidates for epilepsy surgery.

PD Dr. med. vet. (habil.) Martin Schmidt
Dipl. ECVN
Klinik für Kleintiere-Chirurgie
Frankfurter Str. 108
35392 Giessen
Martin.J.Schmidt@vetmed.uni-giessen.de
Vestibular disease

PD Dr. med. vet (habil.) Martin Schmidt

The vestibular apparatus

The peripheral vestibular system, which is the system of balance lies within the petrous portion of the temporal bone. It consists of 5 distinct organs: three semicircular canals transmitting angular acceleration movements (head rotations) and the two otolith organs (utricle and the saccule) that are sensitive to linear (or straight-line) acceleration movements in the horizontal plane (forward-backward-, left-right movement). The saccule senses motions in the sagittal plane (up-down movement). The vestibulocochlear nerve carries information from the semicircular canals, utricle, and saccule towards the vestibular nuclei in the brainstem, the central components of the vestibular system.

The vestibular system maintains the visual image by stabilizing the eyes during head movements utilizing phasic or tonic vestibulo-ocular reflexes. Furthermore it stabilizes the head and neck via vestibulospinal reflexes.

Disorders of the vestibular system can produce varying degrees of loss of equilibrium leading to clinical ataxia. Other signs include falling, head tilt, circling, jerk nystagmus, and positional (vestibular) strabismus. The disturbance is unilateral on the side of the injured system and may result from either central (brain stem) or peripheral (labyrinth) disease. Dizziness and loss of balance can cause excessive drooling, nausea and vomiting. It is important to differentiate central from peripheral disease because of the differences in treatment and prognosis.

Differential diagnosis

The peripheral form of vestibular disease is much more common than the central form. Causes of the condition can include chronic and recurrent inner and middle ear infections, trauma from head injury, tumors, polyps, hypothyroidism, as well as certain drugs like the aminoglycoside antibiotics, including drugs like amikacin, gentamicin, neomycin, and tobramycin. Loop diuretics and also certain ear cleaners that should not be used with ruptured eardrums but accidentally are used can all result in the condition.

The disease can be present from birth as a congenital defect. Congenital vestibular disease is usually seen between birth and three months of age. Breeds predisposed to this condition include the German shepherd, Doberman pinscher, Akita, English cocker spaniel, beagle, smooth fox terrier, and the Tibetan terrier. It can also occur as an idiopathic disease especially in elderly dogs.

Causes of central vestibular disease (the less common form) include inflammatory brain disease (Granulomatous meningoencephalitis, GME), infection, trauma or hemorrhage, hypotonus, and neoplastic disorders.
Treatment

Nausea and vomiting should be alleviated with centrally acting antiemetics. The pets require supportive therapy in the form of nursing care and confinement.

Puppies born with congenital vestibular disease issue often adapt using their visual system. In geriatric dogs, the condition usually resolves in one to two weeks, though the tendency to tilt the head can remain for a lifetime. Inner ear infection should be aggressively treated with antibiotics. If an underactive thyroid is the cause, the vestibular disease will resolve when the metabolic condition is managed correctly. Brain inflammation like GME can be treated using chemotherapy. Prognosis depends on the nature of the disease.

PD Dr. med. vet. (habil.) Martin Schmidt
Dipl. ECVN
Klinik für Kleintiere-Chirurgie
Frankfurter Str. 108
35392 Giessen
Martin.J.Schmidt@vetmed.uni-giessen.de
NEW ASPECTS OF FELINE EPILEPSY

Clinic for Internal Medicine, University of Veterinary Medicine, A 1210 Vienna, Austria

akos.pakozdy@vetmeduni.ac.at

Introduction

The clinical veterinary literature about epilepsy in cats is less extensive than for dogs. The etiological classification is similar in both species basically: idiopathic epilepsy, structural epilepsy, cryptogenic epilepsy (also called probable symptomatic epilepsy) and reactive epileptic seizures.

Rediscovery of temporal lobe epilepsy in cats

Some earlier publications mentioned a specific type of seizure in cats, “twitching limited to the face” or “glazed look with facial twitching” (1, 2). Recently, feline complex partial seizure (CPS) with orofacial automatism (FEPSO) was introduced as a localization-related seizure type based on clinical observation. FEPSO can be recognized clinically as cats show very typical ictal clinical signs. The main signs are: salivation, facial twitching, lip smacking, chewing, licking, swallowing, motionless staring (arrest) (3). Many cats with such seizures have a lesion within the temporal lobe mainly in the hippocampus. This clinical observation suggests that the temporal lobe is the main source of epileptic discharges; however, EEG confirmation was available only in exceptional cases (4).

Despite of the lack of confirmation of the origin of epileptic activity in most cases it is likely that FEPSO is a clinical manifestation of epileptic discharges in the temporal lobe. Feline temporal lobe epilepsy (FTLE) is namely a well-known model from experimental research (5, 6). The characteristic ictal signs are orofacial automatisms, such as salivation, facial twitching, head nodding, and head turning, and these may progress into generalized convulsive motor seizures. Sato (1975) observed that the
chronology of ictal seizure signs is always similar. A staging system was developed. Stage 1 - attention response, stage 2 – immobility, stage 3 – autonomic manifestation, stage 4 – facial twitching and mastication, stage 5 – tonic extension of the contralateral forepaw, stage 6 – generalized clonic convulsion (7). Using clinical and experimental knowledge it can be concluded that TL epileptic seizure is the first localization-related seizure type in small animal practice.

**Hippocampal necrosis/sclerosis (HN/HS) is not an etiological entity**

Hippocampal necrosis (HN/HS) was reported to be frequently present in cats with epilepsy(1). Another study stated that HN/HS is an etiology of epileptic seizure (8). The condition was observed in Switzerland, Germany, Italy, Austria, UK, Australia and the USA as well and it is likely a worldwide phenomenon. Such patients usually show acute cluster seizures and other signs as salivation and behavioral changes. As far as it can be assessed the most signs are consistent with the aforementioned FEPSO. The main histological changes are necrosis and sclerosis at the cornu ammonis (CA) of hippocampal formation. The etiology may be different: vascular, inflammatory, toxic, congenital developmental, neoplastic causes were published, in addition seizures itself may cause HN/HS as well (9, 10, 11, 12, 13, 14). It seems that the HN/HS is a bystander morphological finding in epileptic cats, and not a disease itself. Different etiological disorders can lead to HN/HS.

**Autoimmune limbic encephalitis**

Recently, an association was found between TLE and antibodies against VGKC-complexes (voltage-gated potassium channel) in cats. In a prospective study, antibodies against VGKC were detected in cats with acute TLE. Five of 14 (36%) cats had VGKC antibody concentrations above the reference whereas no increased
antibody concentrations could be found in the 19 control cats, suggesting that the detected immunoglobulins are associated with the condition. Analysis of sera from cats in remission showed that the antibody titer had returned to the reference. The target of the immunoreaction was not the VGKC complex itself, but an associated protein the LGI1 (leucine-rich glioma-inactivated). The study suggests that autoimmune LE might be common in cats (15).

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Peripheral neuropathies and neuromuscular disorders

PD Dr. Michael Leschnik

Disorders of the peripheral nervous system are much more common in companion animals than one would expect. Regarding anatomical and functional classification of peripheral neuropathies we should distinguish between lesions of the cell body (mostly located in the spinal cord), the axon (what we call the peripheral nerve) and the neuromuscular junction. According to the VITAMIN-D system several reasons for peripheral neuropathies are described: trauma (hit by car, high-rise syndrome, stretch injury), immune-mediated (idiopathic polyradiculoneuritis, myasthenia gravis, systemic lupus erythematosus), and metabolic (hypothyroid, diabetes mellitus), toxic (Vincristine), hypoxic (aortic thrombosis), neoplastic (schwannoma, neurofibroma), paraneoplastic (lymphoma, thymoma, insulinoma), or infectious (e.g. neosporosis, toxoplasmosis).

Clinical symptoms include weakness and sometimes also a stiff gait during exercise. Spinal reflexes are reduced or absent and muscle tone is reduced, too. Five to seven days after nerve injury denervation atrophy of the skeletal muscles begins leading to partial or complete replacement of muscle tissue into connective tissue. This might lead to permanent contraction of body parts and the inability to move joints. In mixed peripheral nerves sensitive fibres may also be affected resulting in reduced sensitivity and ataxia when limbs are involved. Regeneration of peripheral nerves may lead to dysesthesia and automutilation in companion animals. Electrodiagnostic technics are able to measure motor nerve conduction velocities (mNCV) or sensory nerve conduction velocities (sNCV) in peripheral nerves under sedation. Alpha motor neurons shall conduct by a minimal velocity of 40m/s, distal axons and cooled axons even slower.

Traumatic neuropathies are a very common example for peripheral axonal damage and regarding the extent of the lesion the subclassification (Sunderland classification) should be mentioned:

First-degree injury (neurapraxia): A reversible local conduction block at the site of the injury. No Wallerian degeneration occurs. This injury usually will recover within hours to a few weeks.

Second-degree injury (Axonotmesis): There is a loss of continuity of the axons within the nerve, with Wallerian degeneration occurring below and slightly proximal to the site of injury. Axons and their myelin sheath are damaged, but Schwann cells, the endoneurium, perineurium and epineurium remain intact. These injuries can heal at about 1mm/day.

Third-degree injury (Neurotmesis): There is a nerve fiber interruption and damage to the endoneurium, but the epineurium and perineurium remain intact. In this case, recovery is variable.
Fourth-degree injury: In this case, there is damage to the axons and the surrounding tissues sufficient to create scarring that prevents nerve regeneration. Only the epineurium remains intact. No nerve conduction passes along the neural pathways in this injured nerve.

Fifth-degree injury: These injuries are usually found in laceration or severe stretch injuries. There is a complete transection of the nerve.

In immune-mediated peripheral neuropathies damage is induced either by autoantibody mediated phagocytosis of the myelin sheet (idiopathic polyradiculoneuritis) or by blockade of postsynaptic acetylcholine receptors (acquired myasthenia gravis). Idiopathic polyradiculoneuritis is common in adult dogs and has formerly been named Coonhound paralysis. It has also been observed in cats and rabbits. Characteristically animals develop muscle weakness in their hind limbs within several hours developing to tetraparesis within one to two days. Tail wagging is not affected and cranial nerves are rarely involved. Sensitivity is intact in all four limbs and spinal reflexes are reduced to absent. Muscle enzymes are usually elevated the first few days of disease. Tentative diagnosis may be supported by electrodiagnostic measurement of nerve root conduction (F-wave). Physiotherapy and supportive care are mandatory; steroids should be avoided as they do not improve symptoms but facilitate muscle atrophy. Recovery usually takes place within several days to three weeks. Unfortunately, single cases are reported that develop respiratory paralysis and should either be euthanatized or put on artificial ventilation.

Acquired Myasthenia gravis is characterized by activity related weakness. Autoantibodies block postsynaptic acetylcholine receptors inhibiting the excitatory effects of the neurotransmitter acetylcholine on nicotinic receptors at neuromuscular junctions and lead to quickly reduced neuromuscular transmission. In 90% of canine cases a megaesophagus is present, implicating possible regurgitation and aspiration pneumonia as severe complication. In several cases paraneoplastic disease has been attributed to this condition and lymphoma, thymoma and sometimes insulinoma are diagnosed. Acetylcholine receptor antibodies can be measured by serology and electrodiagnosis can be achieved by detection of decremental conduction. The tension test requires the intravenous administration of edrophonium chloride or neostigmine, drugs that block the breakdown of acetylcholine by cholinesterase (acetylcholinesterase inhibitors). This test may lead to life-threatening bradycardia which requires immediate atropine administration. Immunosuppressive therapy and removal or reduction of a possibly present neoplasia can reduce antibody production and result in clinical improvement. Supportive therapy in cases of megaesophagus includes elevated feeding or feeding and drinking during sitting.

Canine hypothyroidism is an endocrine disorder that may result in peripheral neuropathy. Hypothyroidism has been associated with the clinical features of myopathy (for example, proximal muscle weakness), mononeuropathy, and sensorimotor axonal polyneuropathy. Large breed dogs and adult dogs are mainly
affected. Vestibular syndrome, facial palsy, trigeminal and sciatic paresis have been described. Behavioural abnormalities (aggressiveness) and neurological symptoms (epilepsy) have also been attributed to reduced thyroid gland function. A lack of thyroid hormones causes reduced mitochondrial activity, resulting in low ATP levels. Cell membrane based sodium potassium pump works inefficiently leading to reduced axonal transports and reduced conduction velocity. Substitution of thyroid hormones leads to clinical improvement within several days in many cases.

Peripheral nerve neoplasia is rare and origins from surrounding tissue: schwannomas from schwann cells or neurofibroma from connective tissue. Especially in cats neural lymphomas have been described. Most common localisation for peripheral nerve tumours are the trigeminal nerve, the radial nerve, and the sciatic nerve. Loss of nerve function within a few weeks is a common finding and especially when the nerve root of the radial nerve is affected ipsilateral ataxia and upper motor neuron disease of the hind limb occur due to infiltration of the spinal cord at the level of the brachial plexus.

Primary infections of peripheral nerves are seen in systemic toxoplasmosis and neosporosis leading to clinical signs only in rare cases. Associated granulomas might be found accidentally during necropsy.