Case Report

jfms OPEN REPORTS

Journal of Feline Medicine and Surgery Open Reports
1–6

DOI: 10.1177/2055116915589840
jfmsopenreports.com
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Ascending haemorrhagic myelomalacia associated with systemic hypertension in a hyperthyroid cat

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Abstract

Case summary An 8-year-old domestic shorthair neutered male cat was presented with acute onset of paraplegia, absent nociception on the pelvic limbs, tail and perianal area, and a previous history of uncontrolled hyperthyroidism (even after thyroidectomy) and chronic hypertension. The magnetic resonance findings (heterogeneous intramedullary ill-defined area, isointense on T1-weighted and hyperintense on short tau inversion recovery and T2-weighted scans between T12 and L5 spinal cord segments) were consistent with ascending haemorrhagic myelomalacia, which was confirmed by histopathology. It also revealed myelomalacia associated with diffuse arteriolar hyalinosis, similar to the reports found with hypertensive encephalopathy.

Relevance and novel information Myelomalacia should be considered as a possible outcome in cats with hypertension. Considering that hypertension is a common consequence of hyperthyroidism, emphasis should be given to blood pressure monitoring, especially after treatment of this condition. We describe the histopathological changes occurring in the spinal cord associated with a state of hypertension.

Accepted: 5 January 2015

Introduction

Although severe hypertension (HT) is relatively uncommon in cats at the time of diagnosis of hyperthyroidism, a significant number will develop HT following the induction of euthyroidism[1] The renin–angiotensin–aldosterone system (RAAS) is upregulated in hyperthyroid cats but, contrary to what was initially thought, might not be the primary pathophysiological mechanism for the development of HT.[2] It is possible that the thyroid hormones cause vascular relaxation, leading to a decrease in effective arterial filling and release of renin as a compensatory response.[2,3] The increase in systemic blood pressure (SBP) is then sustained by cardiac hypertrophy caused directly by HT and by the effects of the thyroid hormone on the local cardiac RAAS.[4,5] The hyperthyroid state also leads to lower filtered and higher absorption of sodium, which, in turn, aggravates HT.[4] Return to the euthyroid state can also lead to the development of HT, probably owing to the inadequacy of the RAAS to respond appropriately to an increase in systemic vascular resistance that occurs with restoration of euthyroidism.[2]

HT associated with hyperthyroidism has been well documented in cats,[6–8] and can be aggravated by renal dysfunction.[9,10] In the feline central nervous system, HT may cause hypertensive encephalopathy, which may lead to neurological signs indicative of intracranial disease.[11] There are a few case reports of cats with systemic HT presenting neurological deficits suggestive of underlying spinal cord disease;[6,9,12–16] but, to date, there are no data regarding the histopathological changes associated

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with systemic HT in the feline thoracolumbar spinal cord. In this case report, we present clinical signs, magnetic resonance imaging (MRI) and histopathological findings of the thoracolumbar spinal cord of a cat affected by systemic HT.

Case description

An 8-year-old neutered male domestic shorthair cat was referred for investigation of acute-onset paraplegia (<12 h). The cat had a history of hyperthyroidism, chronic HT and ataxia. Based on the clinical presentation and increased total thyroxine (T4) 20 months prior to referral, the cat was diagnosed with hyperthyroidism. Increased serum urea and phosphorus was also detected. Treatment with carbimazole (Vidalta; Intervet) 10 mg q24h was initiated but, owing to a low lymphocyte count (0.76×10^9/l; reference interval [RI] 1.5–6.5 $\times$ 10^9/l), was discontinued after 2 months. At that time, a heart murmur was also detected. In the following month the cat presented with dyspnoea, a low lymphocyte count (0.85×10^9/l) and urine specific gravity (USG; 1.025; RI 1.030–1.040), and increased urea, phosphorous and total T4. Cardiac assessment revealed septal systolic bulge assumedly responsible for the heart murmur that was attributed to hyperthyroidism. Atenolol (Wockhardt) was initiated at 1.5 mg/kg q24h for 3 days and followed by unilateral thryroidectomy.

Fourteen months later, the cat was presented to the referring veterinarian with an ataxic gait that was attributed to arthritis but that was non-responsive to non-steroidal anti-inflammatory drugs. On cardiac assessment, a heart rate of 228 beats per minute (bpm) with a gallop rhythm was noted on physical examination. There was also decreased body weight and HT (systolic 208 mmHg, diastolic 140 mmHg, mean pressure 140 mmHg [average of five measurements]). Ophthalmic examination revealed bilateral mydriasis, pupillary light reflexes present bilaterally, bilateral retinal haemorrhage and retinal detachment on the left eye. Lymphocyte count was still low (0.73×10^9/l) and there was a high level of urea, phosphorous and total T4. The treatment initiated consisted of amlodipine 0.267 mg/kg q24h and carbimazole 15 mg q24h, which was successful in decreasing the SBP and total T4 but the urea remained high (19 mmol/l; RI 2.5–8.0 mmol/l). Twenty months after the initial presentation, the paresis and spinal ataxia progressed acutely (<12 h) to paralysis. The average SBP recorded by the referring veterinarian was as follows: systolic 162 mmHg, diastolic 96 mmHg and mean 119 mmHg.

At the time of referral, the cat showed a depressed mental status. Cranial nerve assessment was unremarkable apart from the menace response, which was absent bilaterally, while vision was partially preserved. Pupillary light reflexes were present (direct and consensual). There was flaccid paraplegia with absent nociception and spinal reflexes in both pelvic limbs. Cutaneous trunci reflex was absent bilaterally caudal to the thoracolumbar junction without signs of hyperaesthesia on spinal palpation. Proprioceptive placing and flexor reflexes were normal in the thoracic limbs. Anal tone and perineal reflexes were absent. The bladder was empty at presentation but after fluid therapy it became easy to express, and there was incontinence due to overflow. There was neither movement nor nociception of the tail. Neurolocalisation was multifocal as the cat presented clinical signs that would be attributed to different regions (forebrain, thoracolumbar and lumbosacral). The main differential diagnosis would include vascular, infectious, inflammatory and metabolic conditions.

The heart rate was >200 bpm and the systolic blood pressure (BP) (CAT Doppler BP Kit; Thames Medical) from the pedal artery was 220 mmHg (mean value obtained from five different readings). The abnormal biochemistry results were as follows: alkaline phosphatase 31 U/l (RI 14–11 U/l; IDEXX Catalyst Dx Analyser), haematocrit 24.8% (RI 30.0–45.0%; IDEXX LaserCyte Dx Analyser), potassium 2.6 mmol/l (RI 3.5–5.8 mmol/l; IDEXX VetStat Electrolyte and Blood Gas Analyser) and chloride 130 mmol/l (RI 112–129 mmol/l; IDEXX VetStat Electrolyte and Blood Gas Analyser).

Systemic HT was diagnosed based on the clinical history, clinical and diagnostic findings, and target organ damage (eg, previously reported ophthalmic findings, SBP measurements and neurological presentation).[17–20] Based on the history, previous biochemistry results and electrolyte values, it is possible that the cat had a degree of renal compromise, despite the fact that at the time of referral, urea and creatinine were within the reference intervals.[21] At presentation, the cat had an empty bladder, which did not allow determination of the USG. After admission and fluid therapy, USG determination would be no longer reliable.

Cardiac remodelling, assessed with ultrasound, was diagnosed as unclassified cardiomyopathy as it consisted of biventricular dilation combined with mild left ventricular free-wall hypertrophy and moderate left atrium dilation in the absence of significant mitral regurgitation and restrictive diastolic physiology of the left ventricle.

Non-sustained left ventricular tachycardia was thought to be related to the increased mechanical load imposed by systemic HT to the myocardium as it regressed over 24 h with a reduction in the systolic blood pressure to 170 mmHg. The reduction in the SBP was obtained by titrating the amlodipine (Istin 5 mg tablets; Pfizer) up to 0.4 mg/kg over a 24 h period.

Approximately 24 h after admission, electrolyte analysis after fluid therapy (Aqupharm 11 Hartmann's Solution for infusion; Animalcare) with 17.5 mEq/500ml potassium (potassium chloride 15% w/v concentrate for

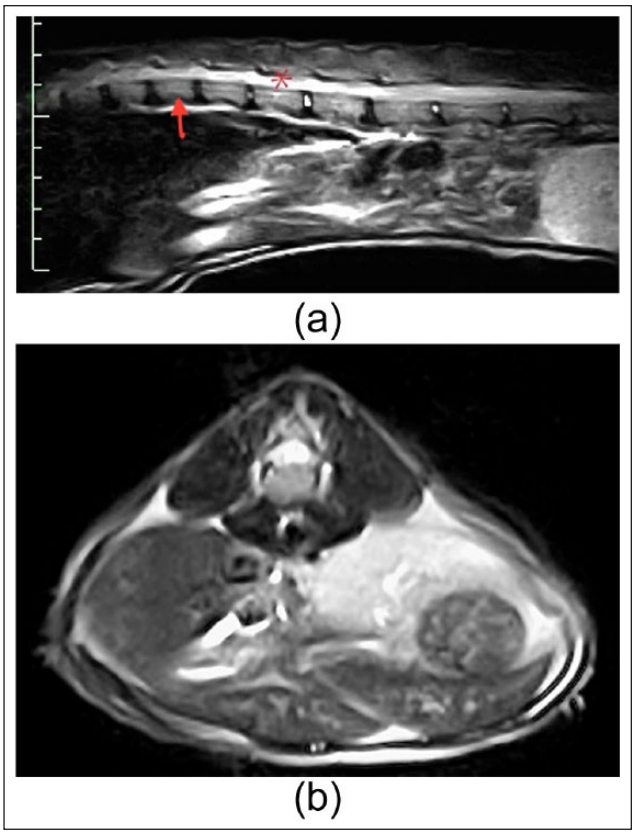

Figure 1 Magnetic resonance images of the thoracolumbar area of the cat reported, showing a heterogeneous, intramedullary ill-defined area, hyperintense on T2-weighted images from the T12 to L5 vertebral levels: (a) FSET2-weighted image (sagittal plane); (b) FSE T2-weighted image (transverse plane at the level of L2). The star indicates the described abnormal area, whereas the arrow marks the T13 vertebra

infusion 10 ml; Mercury Pharma) added revealed the following: Na^+ 171 mmol/l (RI 150–165 mmol/l), K^+ 3.1 mmol/l (3.5–5.8 mmol/l) and Cl^- 135 mmol/l (112–129 mmol/l). The electrolyte imbalance was attributed to fluid therapy.[22,23]

MRI (0.3 Tesla Vet-MR Grande; Esaote) of the thoracolumbar spine was carried out in three planes of orientation, before and after intravenous administration of 0.1 mmol/kg gadolinium (Magnevist; Schering). Precontrast sequences included T1-weighted, T2-weighted and short tau inversion recovery (STIR) images, whereas only T1-weighted sequences were performed after administration of contrast. A heterogeneous, intramedullary ill-defined area, isointense on T1-weighted and hyperintense on STIR and T2-weighted images was visualised extending from the T12 to L5 vertebral levels (Figure 1a,b). There was no enhancement after the administration of gadolinium. Differential diagnoses for the MRI findings included oedema, haemorrhage, inflammation/infection, neoplasia, haemorrhagic myelomalacia and ischaemic myelopathy. Over the following 24 h it was noted that the cutaneous trunci reflex was only present bilaterally, cranial to the

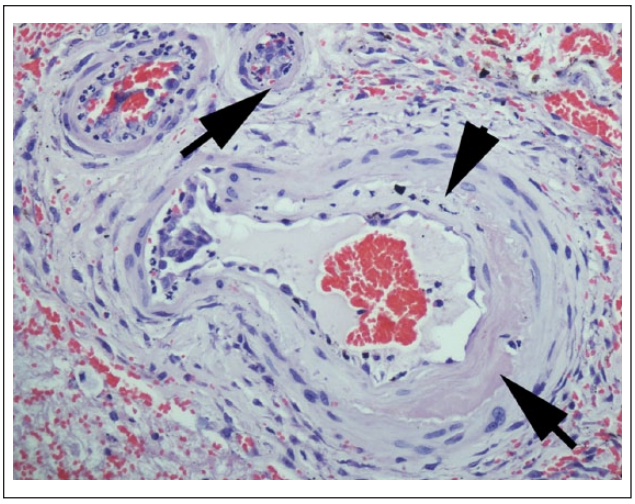

Figure 2 Lumbar spinal cord segment. Deposition of hyaline material (arrows) and associated calcium concretion (arrow head) in the wall of leptomeningeal arterial blood vessels. The endothelial cells show hypertrophic changes (haematoxylin and eosin, × 20)

mid-thoracic area. The remainder of the neurological and physical examination was unchanged. Ascending haemorrhagic myelomalacia was suspected based on the clinical presentation, MRI findings and neurological progression,[24,25] and, in view of the poor prognosis and with the owners' consent, the cat was euthanased.

The thoracolumbar spinal cord was removed from the spinal canal and routinely fixed in neutral-buffered 10% formalin for routine histological examination. Macroscopically, the spinal cord showed diffuse subarachnoid haemorrhagic infiltration, which was more pronounced in L3–L6 spinal cord segments. The haemorrhagic discolouration tended to involve the spinal cord parenchyma producing loss of grey and white matter distinction in the last segments. Brownish parenchymal discolouration occurred also in T12–L2 spinal cord segments, localised in the dorsal quadrant. Histological examination of this lesion revealed a diffuse severe subarachnoid haemorrhage in all the segments. This lesion was associated with arteriolar hyalinosis (Figure 2), occasional extravascular or intravascular calcification and mild neutrophilic infiltration. Occasionally, subarachnoid haemorrhage was associated with large blood lacunae producing severe compression of the underlying spinal cord parenchyma. Spinal cord segments from L2–L6 showed haemorrhagic myelomalacia, which, cranially, became haemorrhagic leucomalacia confined to dorsal funiculi. Moreover, severe degeneration occurred in both the extra- and intradural tracts of spinal nerve roots. At the L4 spinal cord segment, an occluding thrombus of the ventral spinal artery was found (Figure 3). The severe spinal cord lesions were assumed to be consistent with a vascular pathology associated with arteriolar hyalinosis and thrombosis. Immuno-histochemistry performed on a 5

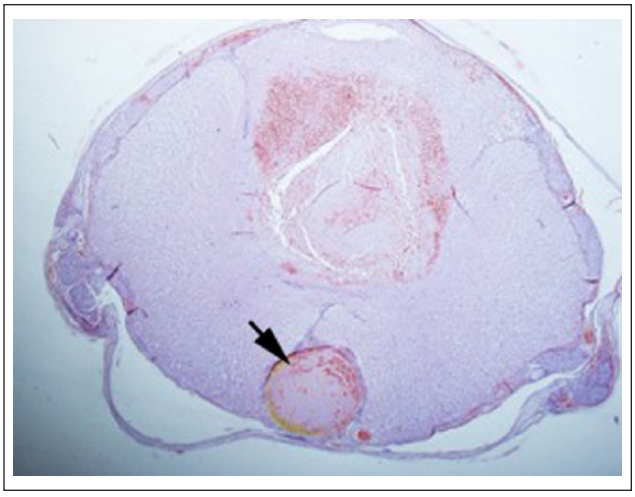

Figure 3 L1 spinal cord segment. Severe haemorrhagic leucomalacia in the dorsal funiculi. Note the thrombus tail in the ventral spinal artery (arrow) (haematoxylin and eosin, × 1.5)

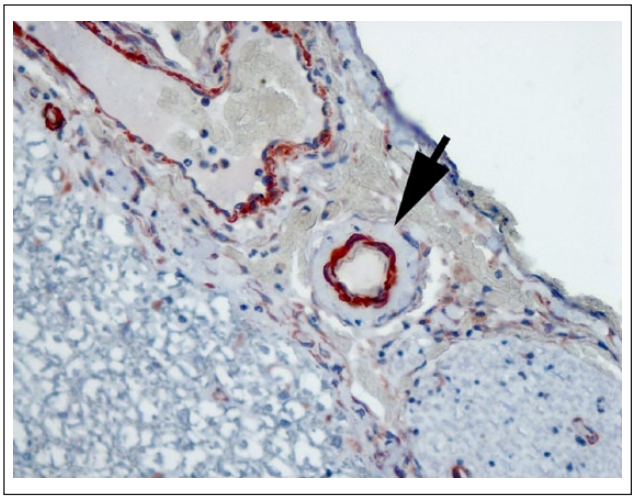

Figure 4 Marked immunoreaction for smooth muscle actin (SMA) expressed by endothelial cells of leptomeningeal blood vessels. One is also affected by hyalinosis (arrow) (immunohistochemistry, ABC method [DakoCytomation], SMA antibody, × 20)

µm fresh frozen paraffin-embedded section (ABC method; DakoCytomation) using mouse monoclonal antismooth muscle actin (SMA) (1:50; clone 1A4 [Dako]) and diaminobenzidine as chromogene showed a strong positivity in intimal cells of leptomeningeal blood vessels lacking of thrombotic events (Figure 4).

Discussion

Hyperthyroidism is proven to cause cardiac hypertrophy,[4,5] increased SBP and sodium retention that aggravates the systemic HT.[5] In the case discussed herein, the cat was suspected to have developed HT after thyroidectomy.[2] Assessment of serum T4 performed postoperatively was still above the RI and compatible with hyperthyroidism, which caused the return to oral medication. It is likely that an euthyroid state was not achieved and HT was undetected when the initial diagnosis of hyperthyroidism was made. We were not able to exclude hyperaldosteronism as a cause of hypokalaemia and HT; however, owing to it being a rare condition, and given the rest of the clinical presentation, this was considered unlikely. At the time of presentation, the ophthalmological examination was not performed given the results provided by the referring veterinary surgeon. The ophthalmological deficits and depressed mental status at presentation were attributed to a suspected hypertensive encephalopathy secondary to hyperthyroidism (although other causes of intracranial disease could not be completely ruled out).

The effects of HT on the brain have been described in two cats in which experimental kidney failure was produced. They included cerebellar herniation, cerebral oedema, arteriolar hyalinosis and hyperplastic arteriolosclerosis.[11] The clinical presentation and the history of the animal, along with the loss of cutaneous trunci reflex over the period of hospitalisation and the hyperintensity on T2-weighted images were consistent with haemorrhagic myelopathy and encephalopathy.[24] The histopathology of the spinal cord revealed severe haemorrhagic myelopathy associated with diffuse arteriolar hyalinosis, which has been previously reported in ischaemic lesions and hypertensive encephalopathy in both human and veterinary medicine.[9,16,26,27] The haemorrhagic lacunae occasionally observed along the T12–L6 spinal cord segments were considered secondary to the ischaemic event or to the hypertensive condition.

As in human medicine, HT is recognised as a major risk factor for cerebral strokes, either infarction or haemorrhage.[28,29] The authors suggest the possibility of, similarly to what happens in human medicine, myelomalacia being caused directly by haemorrhage rather than an ischaemic event secondary to HT. Ischaemic myelopathy generally presents at a different age,[14,15], has a predilection for the cranial cervical spinal cord,[14,15] a good/guarded prognosis[14] and different MRI description of the lesion.[15] Also, in one report,[14] HT is given as a potential cause for ischaemic myelopathy but there is no indication of the duration of the clinical signs. In another report,[15] the cats diagnosed with HT had a BP >180 mmHg but it is unknown how high the BP was and for how long.

A recent study describing the histopathological findings of five cats with ischaemic myelopathy did not reveal any signs of calcification.[16] Included in this sample were two cats: one presented with hyperthyroidism and the other with moderate chronic renal disease. In human medicine HT has been positively correlated with calcification of the blood vessel walls,[30] a finding also revealed by our observations, and calcification with the formation of thrombus and ischaemia.[31] Also, the diffuse positivity to SMA antibody expressed by intimal cells of leptomeningial blood vessels might suggest an ongoing

process of angiotensin-induced transformation of endothelial cells predisposing to neointimal deposition and thrombosis,[31,32] a change also seen in hypertensive encephalopathy.[11]

In the case under study, the histopathology findings were similar to those already reported in the brain of cats with experimentally induced systemic HT and hypertensive encephalopathy,[11,33] and in the cervical spinal cord and ventral brainstem of cats with underlying mild HT, chronic renal disease and mild hypertrophic cardiomyopathy.[16] Although there is no evident direct correlation between vessel degeneration and HT,[16] we suggest that the arteriolar hyalinosis, perivascular calcification, subintimal deposition of smooth muscle cells and thrombosis could have been secondary to the underlying HT. Based on the clinical presentation and information collected, the importance of SBP measurements, prior and after treatment of hyperthyroidism, is clear, even when cases lack clinical signs that implicate hypertensive encephalopathy. In addition, clinicians should be aware that HT may be associated with vascular pathology in the thoracolumbar spinal cord, which may result in severe and irreversible spinal cord injury and associated ascending haemorrhagic myelomalacia.

Conclusions

Myelopathy may be associated with systemic HT and should be included as a possible cause in cats presenting with neurologic signs of acute spinal cord disease and as a possible outcome in cats with conditions predisposing to HT.

Acknowledgements We thank Nicole Baker for referring this case and Catherine Harris for her invaluable advice when reviewing this case.

Funding The authors received no specific grant from any funding agency in the public, commercial or not-for-profit sectors for the preparation of this case report.

Conflict of interest The authors do not have any potential conflicts of interest to declare.

References

1 Morrow LD, Adams VJ, Elliott J, et al. **Hypertension in hyperthyroid cats: prevalence, incidence and predictors of its development**. ACVIM Forum AND Canadian Veterinary Medical Association Convention; 2009 Jun 3–6; ACVIM, Montreal, Canada, 2009, abstract 48, p 699.

2 Williams TL, Elliott J and Syme HM. **Renin-angiotesin-adosterone system activity in hyperthyroid cats with and without concurrent hypertension**. *J Vet Intern Med* 2013; 27: 522–529.

3 Carrillo-Sepulveda MA, Ceravolo GS, Furstenau CR, et al. **Emerging role of angiotensin type 2 receptor (AT2R)/Akt/NO pathway in vascular smooth muscle cell in the hyperthyroidism**. *PLOS ONE* 2013; 8: 1–9.

4 Barreto-Chaves MM, Carrillo-Sepulveda MA, Carneiro-Ramos MS, et al. **The crosstalk between thyroid hormones and the renin-angiotensin system**. *Vasc Pharmacol* 2010; 52: 166–170.

5 Vargas F, Rodriguez-Gomez I, Vargas-Tendero P, et al. **The renine-angiotensine system in thyroid disorders and its role in cardiovascular and renal manifestations**. *J Endocrinol* 2012; 213: 25–36.

6 Morgan RV. **Systemic hypertension in four cats: ocular and medical findings**. *J Am Anim Hosp Assoc* 1986; 22: 615–621.

7 Kobayashi DL, Peterson ME, Graves TK, et al. **Hypertesion in cats with chronic renal failure or hyperthyroidism**. *J Vet Intern Med* 1990; 4: 58–62.

8 Elliott J, Barber PJ, Syme HM, et al. **Feline hypertension: clinical findings and response to antihypertensive treatment in 30 cases**. *J Small Anim Prac* 2001; 42: 122–129.

9 Littman MP. **Spontaneous systemic hypertension in 24 cats**. *J Vet Intern Med* 1994; 8: 79–86.

10 Williams TL, Peak KJ, Brodbelt D, et al. **Survival and development of azotemia in hyperthyroid cats**. *J Vet Intern Med* 2010; 24: 863–869.

11 Brown CA, Munday JS, Mathur S, et al. **Hypertensive encephalopathy in cats with reduced renal function**. *Vet Pathol* 2005; 42: 642–649.

12 Maggio F, DeFrancesco TC, Atkins CE, et al. **Ocular lesions associated with systemic hypertension in cats: 69 cases (1985–1998)**. *J Am Vet Med Assoc* 2000; 217: 695–702.

13 Atkins C. **How I treat hypertension**. *Vet Focus* 2012; 22; 17–23.

14 Theobald A, Volk H, Dennis R, et al. **Clinical outcome in 19 cats with clinical and magentic resonance imaging diagnosis of ischaemic myelopathy (2000–2011)**. *J Feline Med Surg* 2013; 15: 132–141.

15 Simpson K, De Risio L, Theobald A, et al. **Feline ischaemic myelopathy with a predilection for the cranial cervical spinal cord in older cats**. *J Feline Med Surg* 2014; 16: 1001–1006.

16 Rylander H, Eminaga S, Palus V, et al. **Feline ischaemic myelopathy and encephalopathy secondary to hyaline arteriopathy in five cats**. J Feline Med Surg 2014; 16: 832–839.

17 Crispin SM and Mould JR. **Systemic hyperyensive disease and the feline fundus**. *Vet Ophthalmol* 2001; 2: 131–140.

18 Brown S, Atkins C, Bagley R, et al. **Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats**. *J Vet Intern Med* 2007; 21: 542–548.

19 Stepien RL. **Feline systemic hypertension. Diagnosis and management**. *J Feline Med Surg* 2011; 13: 35–43.

20 Jepson R. **Feline sistemic hypertension – classification and pathogenesis**. *J Feline Med Surg* 2011; 13: 25–34.

21 Grauer GF. **Early detection of renal damage and disease in dogs and cats**. *Vet Clin North Am Small Anim Pract* 2005; 35: 581–596.

22 Biondo AW and de Morais HA. **Chloride: a quick reference**. *Vet Clin North Am Small Anim Pract* 2008; 38: 459–465.

23 Willard M. **Therapeutic approach to chronic electrolyte disorders**. *Vet Clin North Am Small Anim Pract* 2008; 38: 535–541.

24 Platt SR, McConnell F and Bestbier M. **Magnetic ressonance imaging characteristics of ascending hemorrhagic myelomalacia**. *Vet Radiol Ultrasound* 2006; 47: 78–82.
25 Okada M, Kitagawa M, Ito D, et al. **Magnetic ressonance imaging features and clinical signs associated with presumptive and confirmed progressive myelomalacia in dogs: 12 cases (1997–2008)**. *J Am Vet Med Assoc* 2010; 271: 1160–1165.
26 Bagley RS, Gavin PR and Holmes SP. **Diagnosis of spinal disease**. In: Gavin PR and Bagley RS (eds). Practical small animal MRI. Ames, IA: Wiley-Blackwell, 2009, pp 123–226.
27 Jellinger K. **Spinal cord arteriosclerosis and progressive vascular myelopathy**. *J Neurol Neurosurg Psychiatry* 1967; 30: 195–206.
28 Johansson BB. **Hypertension mechanisms causing stroke**. *Clin Exp Pharmacol Physiol* 1999; 26: 563–565.
29 Iadecola C and Gorelik PB. Hypertension, angiotensin, and stroke: beyond blood pressure. Dallas, TX: American Stroke Association, 2003
30 Jensky NE, Criqui MH, Wright MC, et al. **Blood pressure and vascular calcification**. *Hypertension* 2010; 55: 990–997.
31 Mandara M. **Meningial blood vessel calcification in the brain of the cat**. *Acta Neuropathologica* 2003; 105: 240–244.
32 Hassler O. **Arterial cell renewal after experimentally induced thrombosis**. *Arch Pathol Lab Med* 1976; 100: 97.
33 O'Neill J, Kent M, Glass E, et al. **Clinicopathologic and MRI characteristics of presumptive hypertensive encephalopathy in two cats and two dogs**. *J Am Anim Hosp Assoc* 2013; 49: 412–420.