COMPANION OR PET ANIMALS

MRI, CT and histopathological findings in a cat with hypovitaminosis A

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ABSTRACT

An adult, male, domestic longhair cat was evaluated for chronic progressive visual impairment and lethargy. Neurological abnormalities localised to the cerebellum/central vestibular system, and optic chiasm/retinas and/or optic nerves were present on clinical examination. MRI and CT studies showed diffuse hyperostosis with thickening of the calvarium and tentorium cerebelli causing compression and distortion of the brain. Biochemical testing showed low plasma retinol levels at 0.1 μmol/l (0.86–2.2). Postmortem examination showed reduction in volume of the frontal lobes secondary to diffuse skull hyperostosis. Microscopically, there were mild white matter spongiosis affecting the corona radiata and optic nerves and multiple small plaque-like thickening of the meninges. This is the first case report to provide a comprehensive clinical, diagnostic imaging and pathological details of hypovitaminosis A in a cat.

BACKGROUND

Vitamin A (retinol) is an essential micronutrient that acts as a systemic antioxidant and contributes to the regulation of a broad spectrum of biological processes. In felids, neurological signs related to vitamin A deficiency are usually progressive and include depressed mental status, seizures, blindness, nystaglia, nystagmus, ataxia, kyphosis, hyperaesthesia and muscle atrophy. This condition has been well documented in wild felids but remains a rare diagnosis in domestic cats.

In this case report, we present a cat with confirmed hypovitaminosis A associated with severe secondary anatomical and pathological abnormalities that have previously been attributed to retinol deficiency in other species.

Hypovitaminosis A is a rare condition in the domestic cat but should be considered as a differential diagnosis in cats presented with multifocal CNS disease (visual deficits and central vestibular signs) and imaging findings compatible with diffuse hyperostosis. In those patients with low serum retinol, the presence of an underlying or concurrent hepatopathy or other systemic disease should be investigated. Once a diagnosis of hypovitaminosis A is established, appropriate therapy including vitamin A supplementation should be promptly started. Even with therapy, severely affected cases may still carry a guarded prognosis.

CASE PRESENTATION

A seven-year-old, male, domestic longhair cat was referred for investigation of a five-week history of lethargy, heat-seeking behaviour, progressive four-limb ataxia and visual impairment. The cat was fully vaccinated and up to date with deworming therapy. The cat had been kept only indoors for approximately five years, with no history of trauma. Since a kitten, it had been exclusively fed on a home-made, cooked chicken-based diet.

At the referring veterinary practice, complete blood count and serum biochemistry profiles showed mild neutropenia (2.06×10⁹/l, reference range 2.5–12.5) and mild elevation of gamma-glutamyltransferase (3 U/l, laboratory reference range 0–1). Feline leukaemia and feline immunodeficiency virus snap tests were negative. Serial systolic blood pressure measurements (Doppler) varied between normotension and mild hypertension, with values ranging between 140 and 160 mmHg. Intraocular pressures were normal at 22 mmHg (left eye) and 21 mmHg (right eye). Funduscopic examination showed areas of tapetal hyper-reflectivity nasal to the head of the optic disc. The optic nerve head appeared darker in both eyes, with a pigmented streak temporal to the optic disc noted bilaterally.

On referral, complete physical examination revealed a very matted coat, flaky skin and bilateral mydriatic pupils. The patient was in appropriate body condition (4/9 body condition score) and weighed 5.7 kg. Neurological examination showed obtunded mentation. On gait analysis, the patient displayed cerebellovestibular ataxia and ambulatory tetraparesis. Postural responses were absent in both thoracic limbs and delayed in the pelvic limbs. The segmental spinal reflexes were normal in all four limbs and the cutaneous truncal reflex was intact. The patient had appropriate muscle tone and size. Cranial nerve examination showed bilateral absent menace response and bilateral reduced pupillary light reflex (direct and indirect). The cat had visual impairment that mainly manifested as difficulty in tracking moving objects. There was bilateral facial hypoalgesia (absent response to nasal septum stimulation) and the corneal reflex was significantly reduced bilaterally. The patient had normal physiological nystagmus (vestibulo-ocular reflex). Based on the neurological examination, multifocal lesions affecting the cerebellum, brainstem, optic chiasm/retinas and/or optic nerves were suspected.

INVESTIGATIONS

In-house blood work measured by an EPOC blood analyser (Alere, USA) was within normal ranges. The cat was premedicated with medetomidine (0.002 mg/kg intravenously; Dormilan, Lintbells,
There was diffuse narrowing of the epidural/subarachnoid space surrounding the cervical spinal cord. The facial and optic nerves had normal shape, size and signal intensity on the volumetric interpolated breath-hold examination sequence. There was no abnormal contrast enhancement after gadolinium (Gadovist, Bayer, UK) administration. The remaining extracranial structures were unremarkable. CT of the skull revealed generalised, increased bone attenuation associated with marked hyperostosis and bone proliferation (figure 2).

Based on the imaging findings, a blood sample was submitted to an external laboratory (IDEXX Laboratories, UK) revealing low plasma retinol levels (0.1 μmol/l, laboratory reference range 0.86–2.2). This confirmed the clinical suspicion of hypovitaminosis A.

DIFFERENTIAL DIAGNOSIS

Nutritional hypovitaminosis A.

OUTCOME AND FOLLOW-UP

Despite administration of dexamethasone (0.21 mg/kg intravenously; Colvasone, Norbrook, UK) and mannitol boluses (500 mg/kg intravenously over 20 minutes, three times 45 minutes apart; Mannitol 20%, Fresenius Kabi, UK), the patient failed to regain spontaneous ventilation following general anaesthesia and was euthanased.

Gross postmortem examination of the cranial cavity and brain confirmed diffuse and bilateral compression atrophy caused by harmonic and moderate overgrowth of the skull bones, in particular the frontal bones. The brain revealed volumetric reduction of the frontal lobes and marked prominence of the olfactory bulbs, secondary to skull compression (figure 3). Throughout the cerebral cortex, the overgrown bone of the cranial vault left an imprint on the cortical GM. Microscopically, in the frontal cortex, there was diffuse mild spongiosis of the white matter and rare swollen axons. There was a mild reduction in laminae cellularity.

Following brain removal, the cerebral dura mater contained numerous, small, pedunculated, plaque-like meningeal masses. Microscopic examination confirmed these to be irregular areas composed of meningeal connective tissue, with cell hyperplasia and mineralisation. Similarly, in the proximal spinal cord (C2), multifocal, poorly defined, thickened areas of dura mater were observed along the proximal spinal cord. In the dorso-lateral fuculi of the spinal cord, scattered degenerate axons were also present.

FIGURE 1  Sequences provided: (A) T2WI mid-sagittal sequence of the brain, (B) VIBE transverse through the tympanic bulla and (C) Constructive interference in steady state (CISS) three-dimensional transverse at the level of C2 vertebral body. There is an abnormal conformation of the brain with compression of the cerebellum (thin arrow), interthalamic adhesion (star) and cervical spinal cord secondary to the abnormal shape/hyperostosis of the skull and vertebrae. The asterisk in image (C) denotes the focal area of T2 weighted hyperintensity compatible with spinal cord oedema secondary to increased intracranial pressure. VIBE, volumetric interpolated breath-hold examination.

FIGURE 2  (A,B) Transverse CT images of the skull in a reconstruction with a bone algorithm (window level: 450, window width: 4500). There is a generalised increased bone attenuation associated with hyperostosis affecting the temporal and occipital bones (small arrows; images (A) and (B), respectively) and tentorium cerebelli (thick arrows on image (B)).
cellularity along the cerebral cortex (chronic cortical atrophy), astrogliosis and satellitosis (figure 4).

The spleen’s silhouette was slightly rounded with red pulp that contained diffuse infiltrates of large round cells; these cells displayed pale, homogeneous, eosinophilic cytoplasm and central to paracentral round nuclei, with coarsely stippled pyknotic chromatin associated with small and indistinct nucleoli. The degree of cellular atypia (anisokaryosis, anisocytosis) of this neoplastic cells was mild and the mitotic index was low (2x10 High Power Field, HPF). Cells were observed either diffusely or as clusters within the lumen of splenic ellipsoids. Macroscopic examination of the liver revealed congestion and moderate enlargement. The portal spaces, especially along the subcapsular parenchyma, were diffusely and severely expanded by the intravascular presence of large clusters of round, neoplastic cells with identical morphological features to those described within the splenic red pulp (figure 4).

The hepatic and splenic neoplastic cell populations were negative for markers of differentiated lymphocytes (CD3 and CD45R), but revealed myriads of intracytoplasmic, metachromatic granules when stained with Toluidine blue. This finding, while supporting a diagnosis of feline systemic mastocytosis (figure 4), was considered incidental in this case.

**DISCUSSION**

Vitamin A (retinol) is an essential micronutrient and systemic antioxidant that is involved in the regulation of multiple biological processes. Vitamin A is also important for stem cell differentiation, organ development and function, innate and acquired immunity, bone remodelling and vision.

There are several reports in the veterinary literature referring to spontaneous and laboratory-induced hypovitaminosis A, with a significant number of case reports referring to captive wild felids. However, hypovitaminosis A remains a rare diagnosis in the domestic cat.

Felids have higher demands for vitamin A when compared with other species due to their inability to convert B carotene to vitamin A. As such, it is suspected that they might be more susceptible to retinol dietary deficiency. In our case, we suspect the origin of the hypovitaminosis A was due to poor dietary intake as retinol concentration is limited in chicken muscle. In lions, a genetic component contributing to the syndrome has been previously suspected.

Neurological signs related to vitamin A deficiency are usually progressive and include depressed mental status, seizures, nystagmus, ataxia, kyphosis, hyperaesthesia, muscle atrophy and nystagmus. Thus, neurological examination generally results in a multifocal CNS localisation.

The degree of pathology secondary to low retinol levels is variable and depends on the severity and duration of the deficiency, hepatic reserves of vitamin A, the stage of skeletal growth at onset of deficiency and other, concurrent nutritional abnormalities. Retinoids may participate in heterotopic bone formation causing progressive and excessive bone growth. Common pathological findings include skull hyperostosis with secondary brain compression and impaired cerebrospinal fluid (CSF) flow; this latter finding has been attributed to partial herniation of the cerebellum and/or impaired CSF reabsorption secondary to thickening of the arachnoid villi. Diffuse myelopathy, secondary to spinal cord compression and elevated CSF pressure, has been suggested in a lion with vitamin A deficiency.

Similar to our case, thickening of the dura mater (secondary to an increase in mucopolysaccharide concentration) has been...
previously reported in calves with experimentally induced chronic hypovitaminosis A.24,25 Maratea and others25 have also reported thickening and focal adhesion of the cervical spinal cord leptomeninges, as well as osseous metaplasia and mineralisation, in a black maned lion with low hepatic vitamin A concentration.

The microscopic findings in the postmortem evaluation of the CNS in our case concurred with previously reported cases of hypovitaminosis A, including cerebral GM astroglialis, Wallerian degeneration of the cerebral white matter,22,28 and possible involvement of the cervical and thoracic spinal cord segments.26

Additionally, changes compatible with the diagnosis of systemic mastocytosis were observed in this cat’s visceral organs such as spleen and liver. Systemic mastocytosis in cats is known to primarily affect the spleen, with subsequent metastatic spread to the liver.30 Despite systemic involvement, mastocytoma is rarely detected on blood smear in cats.31 In this case report, no causative link was observed between the low retinol level and the systemic mastocytosis.

The changes seen in the hippocampus in this case are supported by previous in vivo research that has shown that vitamin A acts as a physiological antioxidant in experimentally induced lipid peroxidation in rat brain and heart cell membranes.32 The hippocampus is especially susceptible to oxidative stress,33 and vitamin A plays an important role in the regulation of the antioxidant balance in this area.34 A previous study revealed that rats fed a vitamin A-deficient diet had an increase in the expression of oxidative enzymes in their hippocampus compared with those fed either a vitamin A supplemented or control diet.34

The cat presented in this report had an abnormal funduscopic examination and impaired vision. Chronic vitamin A deficiency can lead to an abnormal appearance of the tapetal fundus, with the formation of a dark brown streak centred in the area centralis.35 This pigmentation causes a reduction of 90 per cent of the rod visual pigment throughout the paracentral retinal region and complete absence in the area centralis.35

Vitamin A stores are located in the liver. Hepatic pathology may result in changes in the retinol concentrations in liver and blood leading to hypovitaminosis A,33,34,36 and may further exacerbate poor retinol dietary intake.

In contrast, a lack of retinol can also lead to liver disease development due to the loss of its hepatoprotective properties.35 Although liver disease was not suspected in this specific case (and therefore a bile acid stimulation test was not performed before our investigations), some degree of impaired liver function cannot be ruled out based on the abnormal mast cell infiltrates noted on histopathology.

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REFERENCES


