

Case Report

Hippocampal Necrosis in a Cat from Australia

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This paper reports findings from a feline case of hippocampal necrosis. A seven-year-old neutered female cat was seen with a history of behavioural change followed by complex focal seizures. The cat was severely pyrexia on presentation and anisocoria was present. It was treated with cooling, intravenous fluid, and phenobarbitone administration which was later changed to levetiracetam. An MRI was performed and revealed findings of a hypointense T1 and hyperintense T2 signal in the hippocampus and inferior temporal gyrus with mild gadolinium uptake, findings which were consistent with previous cases of hippocampal necrosis. The cat was witnessed to vomit and aspirate 24 hours after diagnosis leading to cardiac arrest and death. Postmortem examination revealed a subacute degenerative encephalopathy involving the hippocampus.

1. Introduction

Hippocampal necrosis is an infrequently reported MRI and postmortem finding in cats [1–6]. It has been predominantly associated with clinical signs of behavioral change and seizure activity and, to date, has been reported in cats from the UK, Switzerland, Italy, USA, and Austria [1–6]. Cats with this disease have been reported to show a myriad of symptoms including salivation, behavioural change, complex focal seizures, facial twitching, lip smacking, chewing, retching, vomiting, diarrhoea, circling, excessive swallowing, and postural deficits or weakness [1–6]. The reported prognosis for this disease is very poor with one case series reporting 4 survivors out of 17 cases (23%) over a four-month period [4].

The closest proposed analogues to hippocampal necrosis in the cat are hippocampal necrosis reported in rats [7], ischaemic hippocampal necrosis in humans [8], and mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) in humans [9]. A study by Barbolt and Everett [7] in rats demonstrated that the majority of rats with hippocampal necrosis had a significant coexisting lesion likely to cause cerebral ischemia, with common lesions consisting of left sided atrial or valvular thrombosis, cerebral thrombosis,

large lymphocyte leukemia, or metastatic mesothelioma. Hippocampal necrosis in the rat was hypothesised to be frequently related to ischaemic injury.

In humans, the hippocampus is found to be the area of the brain most sensitive to ischemia and can be selectively damaged by this state [8]. MTLE-HS in humans is a disease with very similar clinical signs to hippocampal necrosis in cats. Similar MRI changes can be seen with the main difference being that MTLE-HS sufferers have less inflammatory change on histopathology than found in feline cases of hippocampal necrosis [9]. The aetiology of MTLE-HS is unknown, but many mechanisms are proposed including glutamate neurotoxicity and mitochondrial dysfunction leading to neuronal cell loss, immune factors leading to cell loss, a genetic predisposition to the disease, or a multifactorial disease process [9]. The accepted treatment of hippocampal necrosis is based on controlling the symptoms of the disease as there are no reports of resolution of lesions. Whilst a case of Hippocampal necrosis secondary to a pyriform lobe oligodendroglioma has been reported in a cat [1], the aetiology of the majority of feline hippocampal necrosis cases remains unknown and cases carry a guarded prognosis.

2. Case Presentation

A seven-year-old neutered female domestic short hair cat presented with a three-day history of behavioural change followed by salivation and a 40-second-complex focal seizure involving the head, neck, and forelimbs. The behavioural change consisted of excessive vocalization, facial territorial marking, and periuria. The cat lived an indoor only lifestyle and was fed with a mixture of commercial wet and dry cat food. There was no history of exposure to toxins.

On physical examination, the cat was agitated, hypersalivating, and severely pyrexia with a body temperature greater than 41 degrees centigrade (>105.8 F). Anisocoria was present with a miotic left pupil. The findings of behavioural change and seizures localised the neurologic lesion to the forebrain; a variety of possible differential diagnoses were considered including diseases of neoplastic, infectious, inflammatory, developmental, degenerative, idiopathic, metabolic, vascular, and toxic aetiology. The cat was immediately started on phenobarbitone (Phenobarbitone sodium 20 mg/0.5 mL; Mayne Pharma Ltd, Salisbury, South Australia) 3 mg/kg IV q12 h, body cooling, and intravenous fluids with Hartmann's solution at an initial rate of 5 mL/kg/hr. Diagnostic testing was initiated with a complete blood count, coagulation testing, and biochemistry panel. Abnormalities found were a mild elevation in albumin, hypernatraemia, and hyperchloraemia with mild eosinopaenia and neutrophilia.

With treatment, the cat's temperature reduced to 39.9 degrees centigrade (103.82 F) over a 4-hour period. Cooling was discontinued and the temperature continued to decrease to the normal range. The anisocoria and salivation also resolved; however, the cat became stuporous. This was considered to be partly related to sedative effects of phenobarbitone, but concurrent CNS disease seemed likely.

An ammonia tolerance test and toxoplasma IgM:IgG antibody and cryptococcus antigen test were performed. The cat was started on clindamycin (Dalacin; Pfizer Australia Pty Ltd, West Ryde, NSW.) 15 mg/kg IV q12 h pending toxoplasma titer results. Results returned within the reference ranges for all of these tests.

Prophylactic thiamine (Vitamin B1 injectable 125 mg/mL; Value Plus Animal Health Care Products Pty Ltd, Girraween, NSW.) supplementation was started at 25 µg/kg s/c q24 h for 3 days. Nutritional support was also started with supplemental syringe feeding as the cat's gag and swallowing reflexes remained intact. Treatment was started with prednisolone sodium succinate (Solu-Delta-Cortef; 1%. Pfizer Australia Pty Ltd, West Ryde, NSW.) 1 mg/kg IV q12 h prior to performing anesthesia for an MRI scan.

A follow-up blood profile was run 24 hours after presentation and prior to the MRI scan. This revealed a decrease in packed cell volume (PCV) to 17% with total protein remaining in the normal range. There was an increase in ALT to 330 µ/L. Given the history of severe hyperthermia on presentation in combination with the initial blood test results, these changes were considered likely to be due to the secondary effects of hyperthermia with haemolysis and cellular breakdown in combination with the dilutional effect

of intravenous fluid administration. Therapy with phenobarbitone was discontinued due to its potential for hepatotoxicity and its sedative effects. Levetiracetam (Keppra, UCB Pharma, Malvern, Vic.) was started at a dose of 20 mg/kg PO q8 h. The decision was made to proceed with an MRI scan as the benefit of diagnosing the CNS lesion was considered to outweigh the risk of anesthetising the anemic patient. CSF collection was not performed at this time but planned for after MRI interpretation (to ensure that there were no changes associated with high intracranial pressure).

The cat proceeded to MRI, sagittal T1, transverse T2, and diffusion weighted images; dorsal STIR and gradient echo images were obtained through the brain, in addition to post-gadolinium dorsal FLAIR and postgadolinium transverse and dorsal T1 weighted images. The ventricles were normal in size and position with no evidence of an intracranial mass lesion. Images through the inferior temporal lobes showed an increased T2 and decreased T1 signal in the hippocampus and inferior temporal gyrus on both sides. This change was associated with very mild enhancement after gadolinium but no definite mass lesion or abnormality was found on the diffusion weighted images. No abnormality was seen elsewhere in the brain. The findings of a hypointense T1 and hyperintense T2 signal in the hippocampus and inferior temporal gyrus with mild gadolinium uptake were consistent with changes reported in cats with hippocampal necrosis [6].

The cat started to exhibit improvement over the next 24 hours with an improved demeanor, return of appetite, and a normal neurologic examination without evidence of focal seizures, pyrexia, anisocoria, or salivation. The cat then suffered an episode of vomiting and aspiration of ingesta followed by the development of cyanosis and cardiorespiratory arrest. Initial resuscitation was performed with intubation, ventilation, and positive inotropes and was successful but was discontinued at the owners' request leading to death. Necropsy was performed.

All organs were grossly normal except for generalized pallor of the hepatic tissue. Histologic changes were present in the brain and most pronounced in the hippocampus with virtual sparing of the rest of the cerebrum. In all sections of the hippocampus, the majority of neurons were hypereosinophilic and shrunken, with nuclear karyorrhexis. Moderate background gliosis and patchy vacuolation of the neuropil were also noted. Capillaries were prominently lined by very plump endothelial cells and, in one section, several vessels within the hippocampus had moderate to marked lymphocytic cuffs which were limited to Virchow-Robbins space. In this section, there were also numerous plump gemistocytic astrocytes, with large nuclei and abundant brightly eosinophilic cytoplasm. No infectious agents or viral inclusion bodies were visible in the sections of brain examined. These findings were suggestive of a subacute degenerative encephalopathy involving the hippocampus and were consistent with previous reports of hippocampal necrosis. A photo micrograph from one section of brain is included in Figure 1.

Histologic changes were present within the liver but limited to the centrilobular area. Changes associated with acute necrosis were present. There was no evidence of

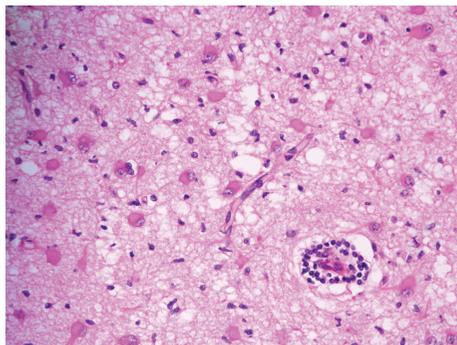


FIGURE 1

inflammation, haemorrhage, or toxic degeneration elsewhere in the liver.

3. Discussion

Hippocampal necrosis is a rare disease in the cat. This case was also complicated by the presence of severe hyperthermia at presentation. The hyperthermia was considered likely to be a secondary complication of the seizure activity and may suggest a longer seizure than was described by the owners or partial upper airway obstruction during the seizure. The aetiology of hippocampal necrosis is not fully understood in animals and may be due to hippocampal ischaemia due to underlying disease [7]. Whilst it is possible that hyperthermia was involved in the aetiopathogenesis of the hippocampal necrosis found in this case. This was considered less likely as behavioural change preceded seizure activity and hyperthermia.

Toxins were considered a possible cause of the original disease process in this cat but seemed unlikely based on history and postmortem findings. Whilst exposure to a cholinesterase-inhibiting compound causes similar presenting signs, in a previous case series cholinesterase activity was unremarkable in all cats with hippocampal necrosis in which the test was performed [5].

The lymphocyte cuffs found in a section of hippocampus may indicate that part of the blood-brain barrier in this region was damaged. It is possible that this is a primary lesion and these cuffs occurred due to an original event which was related to the hippocampal necrosis, but it is also possible that these are a change secondary to hyperthermia.

Elevations in ALT could have been related to hepatocellular injury or enzyme induction. This change was considered to be another effect of hyperthermia and most likely related to processes involving hepatocellular injury. The centrilobular necrosis found on histologic liver examination is typical of “shock necrosis”; this along with an ammonia tolerance test within the reference range suggests that the hepatic changes were secondary to other systemic disease rather than a primary cause of encephalopathy. The rapid elevation in ALT did raise concerns about phenobarbitone administration, as this drug has been identified as a potential hepatotoxin [10]. Phenobarbitone would be contraindicated with severe liver

disease of any aetiology and so the decision was made to change from anticonvulsant therapy with phenobarbitone to levetiracetam which is excreted predominantly in an unchanged form and considered a safer option for patients with hepatic disease [11]. Although unlikely, a thiamine deficiency was considered possible. Thiamine is essential for neuronal glucose metabolism and often deficient in times of increased metabolic demand [12]. Thiamine deficiency has been reported to cause symptoms of seizures, behavioural change, and ataxia in cats [13] so supplementation was considered appropriate in this case.

Hippocampal necrosis is reported to have a poor prognosis with high rates of death and euthanasia [1–6]. The outcome of this case is disappointing, but the management of this case was similar to the four reported surviving cases which were all managed with an anticonvulsant and supportive care [5]. The disease aetiology remains a mystery with many possible proposed mechanisms. Whilst neoplasia has been suggested as a possible cause of some cases of Hippocampal necrosis in cats [1], this was not found in this case at MRI or necropsy.

Hippocampal necrosis has not previously been reported in the southern hemisphere; finding this disease in Australia confirms that it is not limited geographically to Europe and the USA. This disease should be considered a differential diagnosis in cats presenting with seizure activity, behavioural change, or anisocoria.

Conflict of Interests

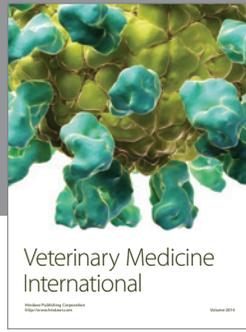
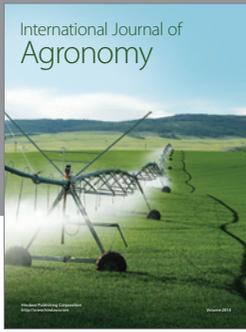
The authors declare that there is no conflict of interests regarding the publication of this paper.

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