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Temporal lobe epilepsy in cats

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ABSTRACT

In recent years there has been increased attention to the proposed entity of feline temporal lobe epilepsy (TLE). Epileptic discharges in certain parts of the temporal lobe elicit very similar semiology, which justifies grouping these epilepsies under one name. Furthermore, feline TLE patients tend to have histopathological changes within the temporal lobe, usually in the hippocampus. The initial aetiology is likely to be different but may result in hippocampal necrosis and later hippocampal sclerosis. The aim of this article was not only to summarise the clinical features and the possible aetiology, but also being work to place TLE within the veterinary epilepsy classification. Epilepsies in cats, similar to dogs, are classified based on the aetiology into idiopathic epilepsy, structural epilepsy and unknown cause. TLE seems to be outside of this classification, as it is not an aetiologic category, but a syndrome, associated with a topographic affiliation to a certain anatomical brain structure. Magnetic resonance imaging, histopathologic aspects and current medical therapeutic considerations will be summarised, and emerging surgical options are discussed.

Introduction

In the last decade, evidence and clinical observations have accumulated in support of spontaneously-arising temporal lobe epilepsy (TLE) in cats. However, the epileptogenic potential of feline temporal lobe structures has been established since the 1930 s. Clinical signs of temporal lobe epileptic discharges were researched in-depth experimentally (Gibbs and Gibbs, 1936) through different stimulation of temporal lobe structures (temporal cortex, hippocampus, amygdala), and the observed clinical signs were very consistent. Orofacial muscle activity is frequently present and includes lip smacking, facial twitching, gagging, tongue movement, hypersalivation and masticatory movement. The ictal progression of the clinical signs follows sequentially, and a six-stage system describes this sequential change (Sato, 1975). The rediscovery of this experimentally-established system and its usage in a clinical setting may lead to a better understanding of TLE (Table 1). The ictal signs can be summarised briefly as orofacial automatisms (Kitz et al., 2017), as this best describes the characteristic ictal signs. However, clearly observable orofacial automatisms are a feature only during stage 3 and stage 4 by Sato. The earlier stages are less obvious and difficult to recognise. Some cats may progress to a higher stage, but not all six stages are visible in a clinical case and individual differences may also exist in the same cat. Many seizures do not progress to the generalised convulsive seizures (stage 6), but it may also occur. Knowledge of this system can increase the veterinarian's awareness and recognition of TLE in cats.

Classification of temporal lobe epilepsy in cats

An aetiological classification of epilepsies is accepted and widely used in the veterinary medicine and very similar in cats and dogs (Berendt et al., 2015). Three main aetiologic categories can be distinguished idiopathic, structural and unknown cause (Pakozdy et al., 2014).

There has previously been controversy concerning the existence of idiopathic epilepsy (IE) in cats, however it is now accepted that IE exists in cats and is defined as a disease in its own right. The aetiology in dogs is genetic or a suspected genetic (Berendt et al., 2015). However,

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Table 1
Staging system of feline temporal lobe epileptic seizures (modified from Kitz et al., 2017).

	Staging system of feline temporal lobe epileptic seizures
Stage 1	Looking around, sniffing, attention
Stage 2	Immobility and staring (arrest)
Stage 3	Orofacial automatism (lip smacking, facial twitching, chewing, swallowing, blinking), hypersalivation, mydriasis
Stage 4	Masticatory movement, facial twitching
Stage 5	Head turning, head nodding
Stage 6	Generalised convulsive tonic-clonic seizure

currently, no genetic background could be confirmed in cats. In feline epilepsy, the term IE has been used interchangeably with epilepsy of unknown origin (EUO). Practically, it is important that a diagnosis of IE (or EUO) is based on a normal interictal clinical and neurological examination. No abnormalities on a diagnostic workup (such as blood work and urinalysis, MRI of the brain and cerebrospinal fluid analysis) should be found. It should, however, be borne in mind that such diagnoses are always connected with an uncertainty, as there is no confirmatory test – and it remains a diagnosis of exclusion (De Risio et al., 2015). This may change if, as in dogs, confirmatory tests become available. Several studies in many cats could not find any aetiology for epileptic seizures, and such cats were classified as IE or EUO. The proportion of such cats within the investigated population were 25% and 37% in the two larger studies (Schriefl et al., 2008; Pakozdy et al., 2010). Recently, a large number of cats with epileptic seizures without interictal deficits were evaluated with advanced diagnostic imaging. The brain MRI was unremarkable in 165/188 (88%; Raimondi et al., 2017). However, subtle changes may have been overlooked without histological examination.

Structural changes in the brain can cause epileptic seizures secondarily, which is why this group was earlier also called secondary epilepsy (SE) or symptomatic epilepsy but is now referred to as structural epilepsy (StE). The age at seizure onset offers some help for differentiation between IE and StE. Older cats (> 7 years) are more frequently associated with StE.

Reactive seizures may represent a further group, including toxic and metabolic causes. Occasionally, this group will be known as having reactive epilepsy, however, this is a misnomer as this is not a brain disease (at least at the beginning). Many veterinarians describe this entity as reactive seizures, which does not clearly state that the aetiology is epileptic. The author suggests using the term reactive epileptic seizures for this group.

A further category is epilepsy of unknown origin, also existed earlier as cryptogenic (probably structural) epilepsy. This group includes veterinary patients with obvious neurological signs but a negative workup. Such cases represent a different group, and are unlikely to be classified into the abovementioned groups. Examples of this category are cats with epileptic seizures and blindness after general anaesthesia with a negative work-up including MRI. This is not IE, as there is an interictal neurological deficit, however, there is no lesion which would justify its inclusion into StE. The classification into epilepsy of unknown cause may be acceptable here, but these cases are different from cases without neurological deficit and with incomplete work-up. Cats with TLE seizures and mild hippocampal MRI changes are also difficult to classify.

It is crucial to understand that feline TLE is not of itself an aetiological category but can arise from many different aetiologies. In fact, the aetiologic factors can be categorised according to the well-known mnemonic 'VITAMIN D', which represents vascular, inflammatory, toxic, anomalous, metabolic, idiopathic, neoplastic and degenerative conditions (Table 2).

Table 2
Possible aetiologies of feline temporal lobe epilepsy.

Category	Disease/aetiology	References
Vascular	Stroke, anaesthetic procedures	Schmidt et al., 1990; Jurk et al., 2001; Altay et al., 2011
Inflammatory	LGI1-associated limbic encephalitis	Pakozdy et al., 2013
Toxic	Kainic acid, tungstic acids	Blum and Liban, 1963; Tanaka et al., 1982
Anomaly	Dentate gyrus malformation	Klang et al., 2015; Chambers et al., 2022
Seizure-induced	Idiopathic epilepsy	Fors et al., 2015
Metabolic	Polycythaemia vera	Kempf and von Magnis, 2019
Idiopathic	Genetic causes are still not confirmed	
Neoplastic	Structural epilepsy	Vanhaesebrouck et al., 2012
Unknown	Many cases of feline hippocampal necrosis	Pakozdy et al., 2011

A further aetiological classification was also introduced initially for human patients (Engel, 2001), but later also suggested for dogs and cats (Podell, 2012). This scheme consists of five axes of seizure investigations: seizure phenomenology, type, syndrome, aetiology and epilepsy associated impairment. Temporal lobe epileptic seizures best fit into the seizure syndrome axis which is a group of signs or other characteristics that define that particular group.

The hippocampal formation, the most characteristic part of the temporal lobe, has a special nature. It is susceptible to epileptic seizures and very epileptogenic itself (Gibbs and Gibbs, 1936). Based on the Hebbian concept 'wire together fire together', the widespread connections of the hippocampus make its neuronal network susceptible to excitotoxic changes (Hebb, 1949). This means that hippocampal necrosis can develop not only from different initial causes, but epileptic seizures within or outside the hippocampus may elicit hippocampal discharges and later hippocampal necrosis. Hippocampal degeneration after an initial injury can contribute to the maintenance and progression of epilepsy in people. In clinical practice, in many cases, the aetiology of hippocampal necrosis and sclerosis often remains unclear and the initial injury undetermined in cats (Table 2).

Temporal lobe epilepsy in humans

Human temporal lobe epilepsy provides a model to better understand feline seizures and epileptic mechanisms. TLE is one of the best understood epilepsy types in human practice and theory (Williams and Marks, 2003; Blair, 2012). In humans, TLE can be divided clearly to the mesial temporal lobe epilepsy (MTLE) and lateral temporal lobe epilepsy (LTLE). The majority of cases have hippocampal or hippocampal-amygdalar seizure onset, but more extended interictal discharging with limbic connection. The MTLE variation has a heuristic importance, being the best understood pathophysiology and is used as a model for understanding focal epilepsies (Pitkánen and Engel, 1996). Several detailed studies exist concerning the ictal electroencephalography (EEG) recorded by foramen ovale electrodes and intracranial strips. Long-term observations have proven a possible progressive outcome by the propagation of seizures to the contralateral anterior hippocampus and the development of bilateral evolution (Halasz, 2016).

In MTLE, it is confirmed that the hippocampal synaptic reorganisation is the long process behind the memory disturbances. The early precipitating injury may be any cerebral damage such as tumour, infection, long duration febrile convulsions, trauma, cavernoma and focal cerebral dysgenetic lesion (frequently), or autoimmune affections.

TLE was the first object for epilepsy surgery, and it was introduced widely in human (Engel, 1996; Jehi et al., 2015). It remains one of the most frequently executed interventions, although the dissection of focal cortical dysplasia has slowly outgrown it, in adults also. The results are

excellent (about 70% seizure free rate) and complications are minimal, apart from the loss of a quadrant of the opposite field of vision.

Therefore, the conclusion is that epilepsy surgery in pharmacological resistant cases can be an excellent option if extensive work-up permits. However, disappointingly for patients and doctors, it was slowly revealed that those proportion of patients who can completely cease anti-seizure medication is much less frequent than had been hoped (around a maximum 25–30%), but they may subsequently become seizure free (Kanner, 2004). The influence of the surgery on socio-economic outcomes is difficult to analyse because of large differences among countries in terms of social, cultural and economic aspects.

There is an endeavour to develop a closed skull variation of the open surgery, but this is still executed in a small minority of places for temporal lobe surgery. There are different presurgical evaluation approaches, and the failures of reaching better results is leading worldwide to the stereoencephalograpic monitoring practice, promising better results in the more precise outline of the seizure onset zone (Fiani et al., 2021).

MRI changes within the temporal lobe

Feline TLE is known for both characteristic clinical and diagnostic imaging features. The MRI often shows changes in signal intensity of the hippocampal region (Classen et al., 2016), which are frequently consistent with hippocampal necrosis on histopathology, but may also be caused by other pathologies, among them sclerosis, oedema, inflammation, ischaemia or a combination of these.

High signal intensity in the so-called water-sensitive MR sequences (T2 and FLAIR – fluid attenuated inversion recovery) represents an elevated water content of the affected structures, in this particular case the hippocampus (Figs. 1 and 2) or the adjacent piriform lobe. It is not possible to define the underlying cause or histopathological changes with MRI alone. Elevated water content can be a consequence of postictal oedema, inflammation together with hyperaemia (such as limbic encephalitis (LE)), neoplasia, focal ischaemia, or sclerosis. In the case of mild T2-hyperintensity, its clear detection is not possible because of subjectivity. Quantitative MR-methods like T2-relaxometry appear to be helpful as shown in human patients (Jack, 1996; Bernasconi et al., 2000) and some suspected cases of canine TLE (Lörincz et al., 2017).

Characteristics other than signal intensity include hippocampal volume changes. Hippocampal sclerosis (Fig. 1), which is described in humans (Cendes et al., 2000) and in dogs (Buckmaster et al., 2002; Lörincz et al., 2021), may represent either a cause or consequence of epileptic seizures together with volume loss/shrinkage of the entire hippocampus or some hippocampal subfields (Kuwabara et al., 2010). If marked or unilateral, it can be subjectively evaluated. In the case of bilaterally symmetrical or subtle unilateral changes, hippocampal volumetry seems to be a valuable tool in its recognition (Milne et al., 2013). Hippocampal asymmetry is also described in cats with limbic seizures (Mizoguchi et al., 2014). Increased volume/swelling of the entire hippocampus has been described in feline hippocampal necrosis corresponding most likely to the acute phase of the disease, consistent with ongoing oedema and hyperaemia, but also in other pathological conditions like intracranial lymphoma (Scalia et al., 2021).

Contrast enhancement is the third property more frequently described in the veterinary than in the human TLE. In human neuroradiology, contrast studies are, in most cases, not part of the MR protocol for TLE, as hippocampal enhancement is not supposed to be evident in human hippocampal sclerosis (Blümcke et al., 2013). Feline hippocampal necrosis seems to be different from that viewpoint – homogenous or heterogenous, mild to severe hippocampal contrast enhancement is a characteristic change, at least in the acute phase of the disease (Fig. 2). There are some inconsistencies in the veterinary literature regarding whether hippocampal contrast enhancement is required (Wahle et al., 2014; Raimondi et al., 2017) or signal changes alone are satisfactory (Pakozdy et al., 2011; Wagner et al., 2014; Classen et al., 2016; Hazenfratz and Taylor, 2018) to acquire an MR-diagnosis of hippocampal necrosis. In a recent study, hippocampal necrosis was histopathologically proven in feline cases of both with and without hippocampal contrast enhancement, suggesting different stages of the same disease (Riegler et al., 2022).

Despite varied evidence from the literature, (Claßen et al., 2016; Scalia et al., 2021; Riegler et al., 2021) MRI remains an important and valuable tool in diagnosing feline hippocampal necrosis. If volume loss is obvious, hippocampal sclerosis is the most likely. Hippocampal contrast enhancement and swelling is a recognised sign for hippocampal

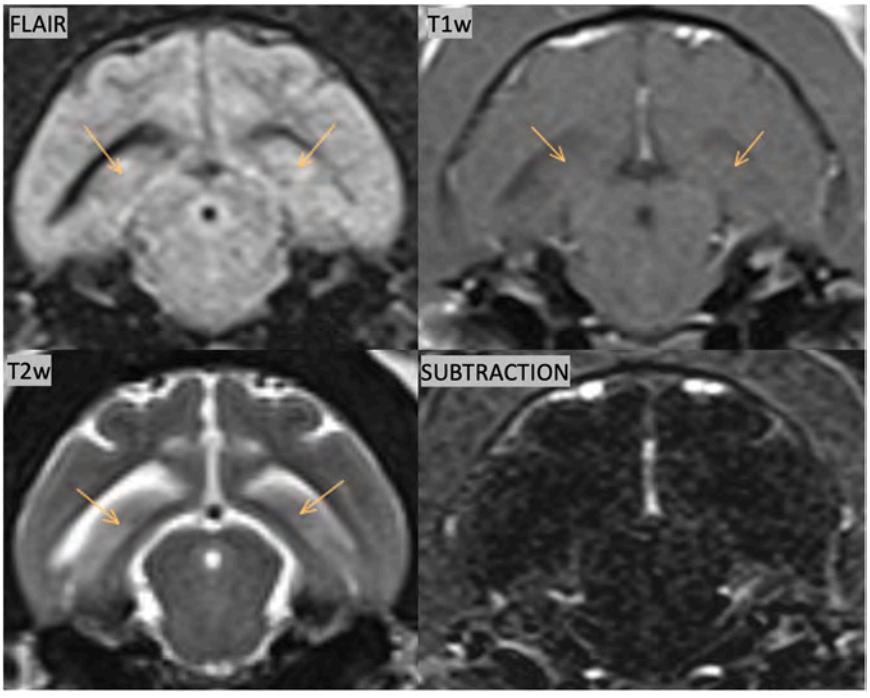

Fig. 1. MRI of hippocampal sclerosis. Transverse FLAIR (fluid attenuated inversion recovery), T2w, T1w and subtraction images. Note the mild hyperintensity of both hippocampi in the fluid sensitive sequences (T2w and FLAIR) and the mild hypointensity in the T1w images (arrows). There is no contrast enhancement of the hippocampi (no hyperintensity in the subtraction image). This together with the mild volume loss of the hippocampi based on the mild dilation of the adjacent lateral ventricles (right > left) suggest hippocampal sclerosis.

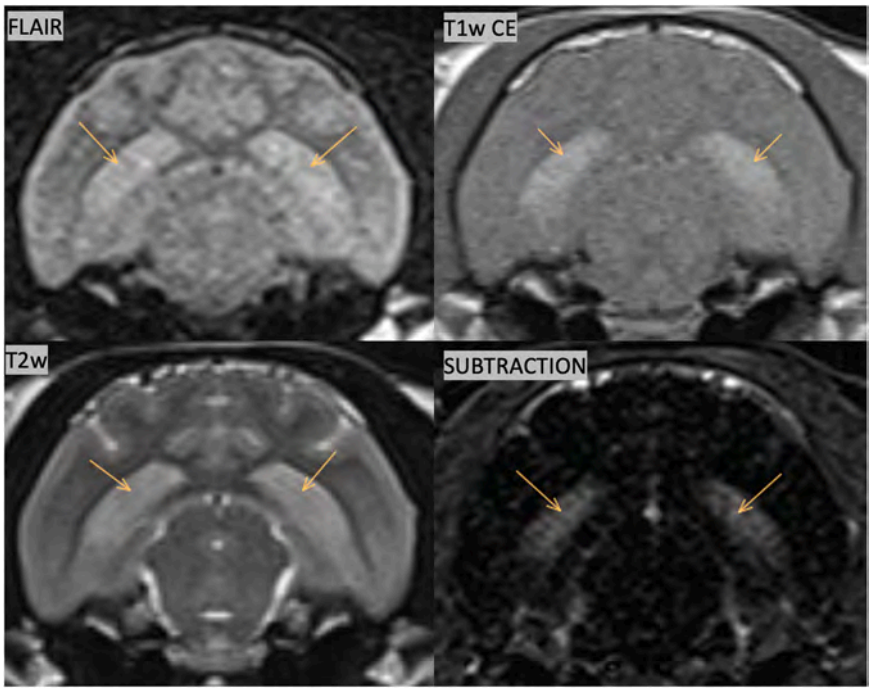

Fig. 2. MRI of hippocampal necrosis. Transverse FLAIR (fluid attenuated inversion recovery), T2w, contrast enhanced T1w and subtraction images. Note the bilateral symmetrical swelling of the hippocampi, so as the hyperintensity in the fluid sensitive sequences (FLAIR and T2w) and the homogenous enhancement in the contrast enhanced T1w and subtraction images (arrows).

necrosis, most likely in an acute phase. However, it should be borne in mind that, based on the MRI, it cannot be clearly differentiated from other aforementioned aetiologies: for example postictal edema is a transient MRI finding, therefore it is expected being resolved in control studies. Unfortunately, serial MRI studies concerning epileptic cats are not currently available.

Histopathological changes within the temporal lobe

Histopathological changes within the temporal lobe, specifically the hippocampus region, are commonly found during neuropathological examination in cats with epileptic seizures. The most common findings comprise uni- or bilaterally localised hippocampal necrosis and hippocampal sclerosis. Hippocampal necrosis (Fig. 3) is characterised by pan-necrosis of neurons and glial cells, affecting one or more segments of the cornu ammonis to varying degrees and sometimes the dentate gyrus as well.

Cats with prolonged or generalised seizures, refractory to antiseizure treatment, commonly present with hippocampal sclerosis (Fig. 4), which is defined by selective subtotal loss of hippocampal neurons together with astrogliosis. Approximately one third of epileptic cats display hippocampal sclerosis in one study (Wagner et al., 2014). Lesions were reported to be predominantly localised in the CA3and CA4 segments in monosegmental types and within CA3 and CA4 in multisegmental distributed cases (Wagner et al., 2014; Matiasek and Rosati, 2017). Dentate gyrus pathology comprises blurring of the granule cell

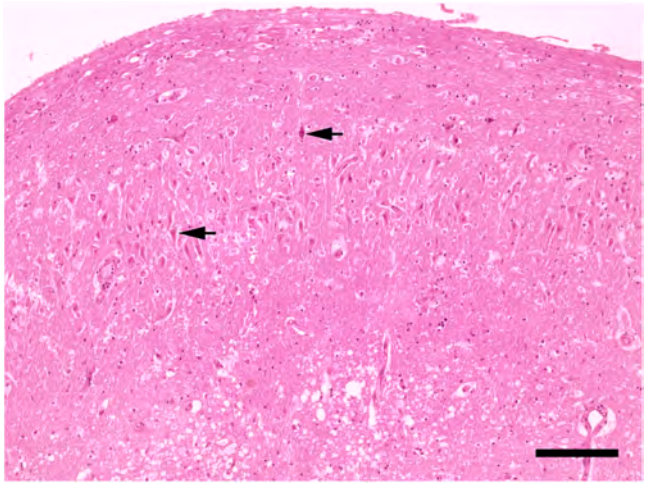

Fig. 3. Cat brain with hippocampal necrosis. Numerous, hypereosinophilic, shrunken, pyramidal neurons with pyknotic nuclei (arrows) within the cornu ammonis. Hematoxylin-Eosin. Note spongy state of the adjacent white matter. Bar = 160 μm.

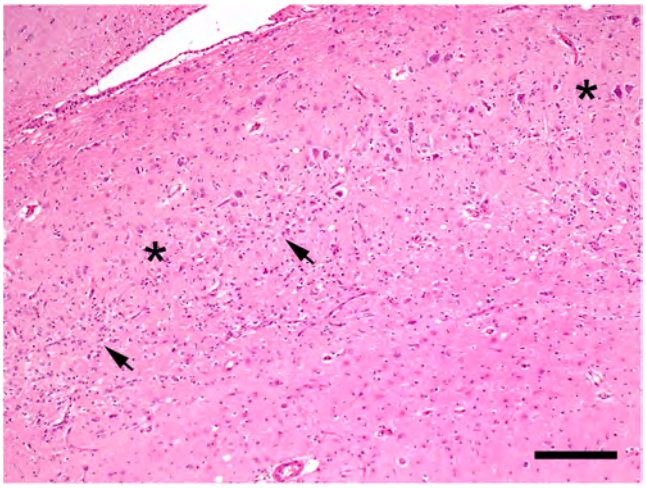

Fig. 4. Cat brain with hippocampal sclerosis. Segmental extensive loss of pyramidal neurons in the cornu ammonis (asterisks) together with astrogliosis, and proliferation of microglia (arrows) and capillary. Hematoxylin-Eosin. Bar = 160 μm.

layer–molecular layer boundary, individual or clusters of ectopic granule cells, gaps of the granule cell layer and bilamination (Wagner et al., 2014). In prolonged cases of TLE, besides volume reduction of the hippocampus, structural alterations of the dentate gyrus including hypergyration and broadening are also described (Klang et al., 2014; Glantschnigg-Eisl et al., 2017) and precipitating events date back months to years and may not be further identified at that time. Hippocampal sclerosis is the most important trigger of progressive epilepsy and may be preceded by hippocampal necrosis. (Pakozdy et al., 2017; Pitkanen et al., 2017; Klang et al., 2018). However, the true prevalence cannot be reliably assessed in clinical settings alone.

Neurodegenerative lesions within the hippocampus region including hippocampal necrosis and hippocampal sclerosis are commonly associated with additional, intra- and extrahippocampal pathologies (Klang et al., 2018) suggesting the latter may serve as an epileptogenic focus in induction and progression of hippocampal neurodegeneration. However, in some cases, it is not clear if additional pathologies could be an incidental finding. Inflammatory conditions predominate and include infectious diseases such as central nervous manifestations of feline infectious peritonitis or cerebral toxoplasmosis, but also non- infectious disorders such as auto-antibody-dependent LE (Klang et al., 2018). LE in cats is a disorder associated in some cases with serum antibodies against cell surface neuronal proteins, specifically leucine-rich glioma inactivated 1 (LGI1; Pakozdy et al., 2013). Histopathological findings include complement activation together with immunoglobulin deposition, which may be accompanied by mild to moderate perivascular and parenchymal lymphocytic infiltrates (Klang et al., 2014), and selective limbic blood–brain barrier breakdown (Tröscher et al., 2017). Furthermore, besides idiopathic cases, intracranial neoplasia such as meningioma and oligodendroglioma are also found simultaneously (Klang et al., 2018).

Antiseizure management in feline temporal lobe epilepsy

The aim of feline epilepsy treatment is to optimise quality of life by minimising epileptic seizure occurrence and antiseizure drug (ASD) adverse effects. In cats with structural epilepsy, treatment of the underlying seizure aetiology (whenever possible) is required in combination with ASDs Fig. 5.

In cats with IE, similar to that recommended by the IVETF for canine IE (Bhatti et al., 2015), ASD treatment should be initiated when the cat experiences at least one of the following: two or more epileptic seizures within a 6-month period; status epilepticus or cluster seizures; worsening of epileptic seizure frequency/severity/duration; or severe or prolonged (e.g. $>$ 24 h) postictal signs.

The ASDs that have been shown to be safe and efficacious in cats are limited to phenobarbital (PB) and levetiracetam (LEV). A systematic review of ASDs' efficacy and safety in feline epilepsy concluded that PB may currently be considered the first line ASD for feline epilepsy (Charalambous et al., 2018). The initial PB dose in cats is 1.5–2.5 mg/kg every 12 h. The PB oral dosage is subsequently tailored to the individual, based on an accurate epileptic seizure diary, serum PB concentration monitoring, as well as occurrence and degree of adverse effects.

Despite the relatively limited published data on the efficacy of LEV in feline epilepsy, LEV use in cats is increasing due to its safety and tolerability and the limited ASD options in cats. LEV has also been evaluated as an adjunctive therapy to PB in cats with presumed IE. The recommended initial dose for LEV as monotherapy or adjunctive therapy in cats is 20 mg/kg every 8 h.

Outcome of feline temporal lobe epilepsy

The prognosis of temporal lobe epilepsy in cats has never been investigated systematically. It is likely that a general prognosis cannot be given due to the many possible causes and highly variable severity of the different conditions. An early publication reported a fatal prognosis for hippocampal necrosis (Fatzer et al., 2000), but this seems to be an oversimplification, and the real prognosis is likely to depend on many factors. The most important factors are: (1) the primary (e.g. underlying) aetiology; (2) how promptly effective antiseizure treatment can be started; (3) how severe the epileptic seizures are; (4) how severe the hippocampal pathology is.

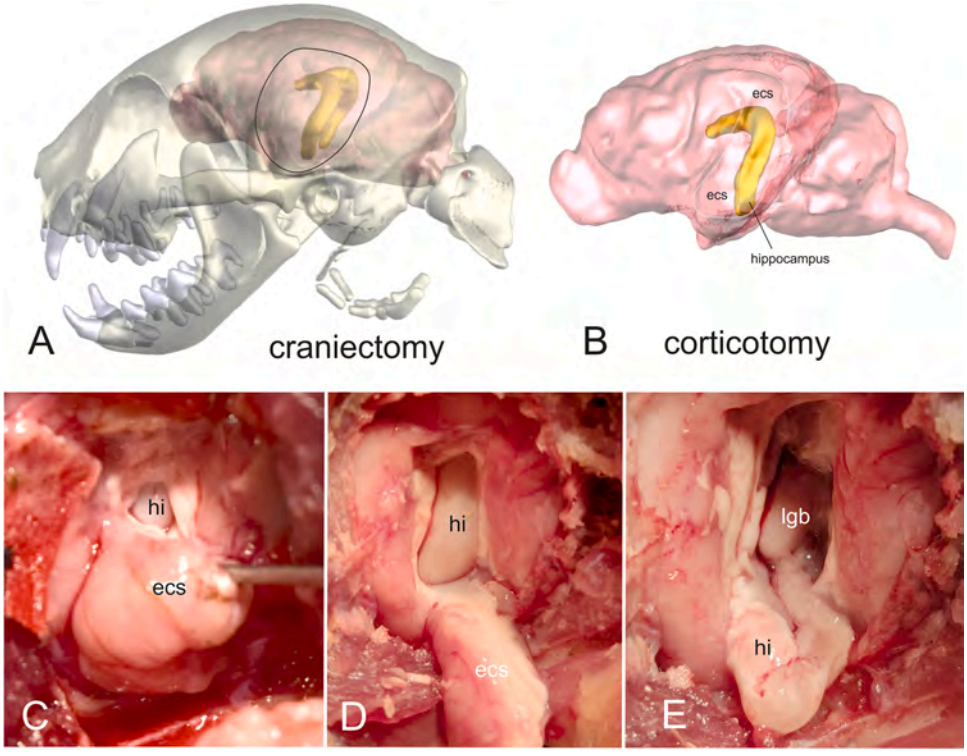

Fig. 5. Surgical technique of partial corticohippocampectomy in cats. After splitting of the temporal muscles, a craniectomy over the caudal sylvian and ectosylvian gyri is performed (A). The dorsal end of the caudal ectosylvian sulcus acts as a leading structure for the incision into the cortical surface (B). The cortex of the ectosylvian gyrus is horizontally transected a couple of mm below the dorsal end of the ectosylvian sulcus (C). The opening in the pallium is ventrally enlarged on each side of the first cortical incision. The parenchyma of the ectosylvian gyrus is further dissected until the temporal horn of the ventricle is exposed (D). A horizontal incision is made in the dorsal part of the exposed hippocampus (hi). The procedure is repeated on the ventral aspect of the exposed hippocampus and the body can be resected en bloc (for a detailed description compare Zilli et al., 2020).

Hippocampectomy in cats

Feline TLE is a unique epilepsy syndrome, as the epileptogenic lesion, epileptogenic zone and symptomatogenic zone are combined in a well-defined part of the brain. This makes affected cats potentially suitable candidates for epilepsy surgery. Resection techniques of partial cortico-hippocampectomy (PCH), that is analogous to anterior temporal lobectomy or selective (amygdalo-) hippocampectomy in humans, have been described with sufficient detail to allow for standardisation of surgical therapy in an early stage of this new intervention (Zilli et al., 2021). Although hippocampectomy has already been successfully performed in a cat with hippocampal atrophy (Hasegawa et al., 2021), the technique is just beginning to emerge in the veterinary field and clinical experience is quite limited. In addition to operative risks and complications, the clinical manifestations of the loss of hippocampal function after PCH will be a major concern for cat owners.

Cats and dogs have been one of the most common experimental animals for ablation studies in the last century. It is known from these and other investigations that the hippocampus formation is the morphological basis of encoding, consolidation and retrieval of memory in the brain of mammals and is therefore vital for learning. In conjunction with neocortical networks, the hippocampus also influences cognitive functions, spatial orientation and emotional behaviours (Kowalska, 1995). Removal of the hippocampus has been associated with deficits in motivation, spatial memory and orienting response, as well as loss of conditioned reflexes and learned behaviours in cats (Teitelbaum, 1964). The described clinical signs observed after ablation of the hippocampus (Kling et al., 1960; Gol et al., 1963; Andy et al., 1967; Brown et al., 1969) were somewhat reminiscent of cognitive dysfunction syndrome observed in older cats (Gunn-Moore et al., 2007). Hyperactivity and undirected aggressive behaviour were also reported. Time and experience with the technique must show if the observed side effects of PCH are acceptable for cat owners.

Conclusions

Temporal lobe epilepsy seems to be outside of the well-established veterinary epilepsy classification, as it is not an aetiologic category, but a syndrome, associated with a topographic affiliation to the hippocampus. With the ongoing seizures functional and structural changes within the hippocampus make the outcome less favourable. Therefore, early and effective treatment is crucial for the good long-term outcome.

Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

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