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Necrosis of Hippocampus and Piriform Lobe in 38 Domestic Cats with Seizures: A Retrospective Study on Clinical and Pathologic Findings

R. Fatzer, G. Gandini, A. Jaggy, M. Doherr, and M. Vandevelde

The clinical records of 38 cats (1985–1995) with a neuropathologically confirmed diagnosis of necrosis of the hippocampus and occasionally the lobus piriformis were evaluated retrospectively. There was no sex or breed predisposition. Most cats were between 1 and 6 years of age (mean age = 35 months) and had either generalized or complex-partial seizures of acute onset and rapid progression. The seizures had a tendency to become recurrent and to present as clusters or even status epilepticus later in the course of the disease. Fourteen cats died spontaneously, and 24 were euthanized. Histopatologic examination revealed bilateral lesions restricted to the hippocampus and occasionally the lobus piriformis. The lesions seemed to reflect different stages of the disease and consisted of acute neuronal degeneration to complete malacia, affecting mainly the layer of the large pyramidal cells but sometimes also the neurons of the dentate gyrus and the piriform lobe. The clinical, neuropathologic, and epidemiologic findings suggest that the seizures in these cats were triggered by primary structural brain damage, perhaps resulting from exitotoxicity. The cause remains unknown, but epidemiologic analysis suggests an environmental factor, probably a toxin.

Key words: Epilepsy; Neuronal degeneration.

In addition to rabies, several other disorders affecting the central nervous system (CNS) have been recognized during the past 3 decades as causes of seizures in cats: feline infectious peritonitis, feline ischemic encephalopaty (FIE), nonsuppurative meningoencephalitis, viral polioencephalomyelitis, and feline immunodeficiency virus (FIV) encephalitis.[1–6] Despite numerous reports, little information exists on the pathophysiology of seizures in cats. Although some authors have stated that idiopathic epilepsy (IE) is an important cause of seizures in cats,[7,8] others have indicated that seizures usually are the result of structural brain diseases in this species.[9–12] A detailed description of the seizures, a complete neurologic examination, and additional diagnostic tests are necessary to rule out IE. This approach may be difficult because most epileptic cats have atypical seizures, and owners may be reluctant to complete a clinical work-up. Here, we describe a feline seizure disorder that is characterized by severe pathology in regions of the limbic system and that was noted first in the early l970s.[13] To our knowledge, no detailed study of this disease has been reported. The purpose of this report is to define the clinical and neuropathologic findings in the disorder.

Materials and Methods

The records of 38 cats with a confirmed histopathologic diagnosis of necrosis of the hippocampus and piriform lobe were evaluated retrospectively. Nine cats were referred to the Institute of Animal Neurology of the Faculty of Veterinary Medicine (Bern, Switzerland) between January 1985 and October 1995. Each cat was subjected to a complete clinical and neurologic examination. Ancillary laboratory procedures included routine hematology and blood chemistry analysis and cerebrospinal fluid (CSF) examination. Further laboratory assays were performed in selected cats, including urinalysis, plasma protein electrophoresis, erythrocyte sedimentation rate, and feline leukemia virus (FeLV) and FIV serum tests. The remaining 29 cats underwent a clinical work-up by the referring veterinarians and were euthanized or died because of severe neurologic signs. All cats were submitted for necroscopy at our institute.

A pathologic examination of the CNS was done in all cats; in addition to the CNS, a general necropsy was performed in 29 animals. The brain was fixed in 4% formalin for 5 days, and coronal sections (4 μ) were stained with hematoxylin and eosin (HE). Selected slides were stained with Luxol fast blue/cresyl echt violet[a] and Luxol fast blue/silver nitrate.[b] Eighteen brains were submitted for rabies diagnosis by immunofluorescence, and 10 cats were evaluated for metaldehyde toxicity.

Results

Epidemiologic Data

Twenty-seven cats were referred from the canton of Bern (n = 14) and the surrounding cantons (n = 13). Eight cats were from other regions of Switzerland, and the origin of 3 cats was not known. The origin of the animals matches the general geographic distribution of the Institute's case material. Cats came from rural and urban areas and presented during all seasons, with a slightly higher frequency during the warmer months. Most cases were sporadic, but 2 small clusters of 2 and 4 animals, respectively, were identified; 2 animals of the latter group could not be examined and therefore are not included in this series. Each of these clusters occurred in 1 village, 1 of them even at the same farm, where the cats became ill around the same time. Specific risk factors were not apparent.

Signalment and History

There was no breed predisposition. Of the affected cats, 36 were domestic shorthairs, 1 was a British Shortair, and 1 was a Birman. The age distribution is presented in Figure 1 and ranged between 3 months and 9 years (mean = 35

From the Swiss Reference Lab for Spongiform Encephalopathies, Institute of Animal Neurology, University of Bern, Bern, Switzerland (Fatzer, Jaggy, Vandevelde); the Department of Veterinary Clinical Sciences, Faculty of Veterinary Medicine, University of Bologna, Bologna, Italy (Gandini); and IVI, Institute for Virus Diseases and Immunoprophylaxis, Mittelhäusern, Switzerland (Doherr).

Reprint requests: Rosmarie Fatzer, Institute of Animal Neurology, Faculty of Veterinary Medicine, University of Bern, Bremgartenstrasse 109a, CH-3012 Bern, Switzerland; e-mail: rosmarie.fatzer@itn.unibe.ch.

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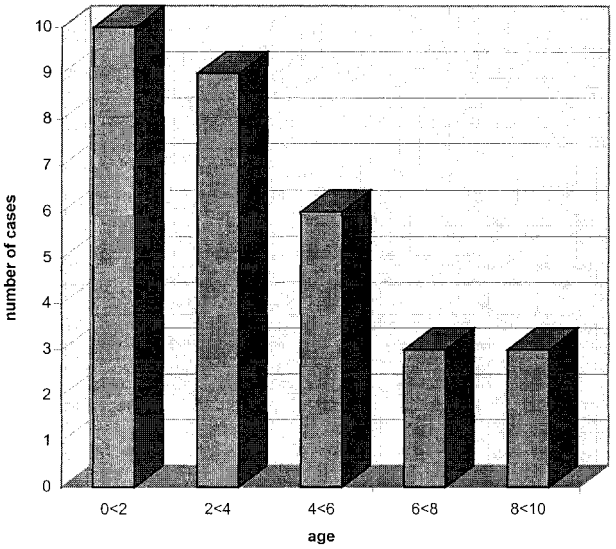

Fig 1. Age distribution (years) of cats with hippocampal necrosis.

months). The majority of the animals were between 1 and 6 years old, and the age of 8 cats was unknown. There were 19 female (12 spayed) and 13 male (9 neutered) cats. The gender of 6 animals was unknown. In most cats (n = 35), there was a history of acute onset and rapid deterioration of clinical signs leading to spontaneous death (n = 14) or euthanasia (n = 24) at the owners' request. Two cats had a subacute progressive course and 2 others were submitted only for necropsy without further information. The duration of the clinical signs ranged from a few hours to 5 days.

Clinical Findings

In some cats, extraneural signs were observed by the owner, including vomiting (n = 3), diarrhea (n = 4), and polyphagia (n = 3). These signs were confirmed by clinical exmination. The neurologic abnormalities are presented in Figure 2. Generalized or partial seizures were observed in most cats (n = 28). Other neurologic signs consisted of behavioral changes such as excessive aggression (n = 19), salivation (n = 13), bilateral mydriasis (n = 7), impaired consciousness (n = 5), decreased menace response (n = 4), decreased or absent postural reactions (n = 3), and absence of physiologic nystagmus (n = 2). Seizures often started suddenly as isolated episodes over a few days and had a tendency to become recurrent, mostly observed as clusters. The intensity and frequency of the seizures increased rapidly in all cats and, in 11 cats, led to status epilepticus and spontaneous death or euthanasia, despite treatment with diazepam, phenobarbital, and pentobarbital.

Characterization of the Seizures

Prodromal signs were observed in more than half of the cats and lasted for an average of 2 hours. These signs were characterized mainly by behavioral changes such as hyperexcitability, aggression, restlessness, anxiety, and salivation. The description of the ictal event was based on video recordings of a few cats including slow motion analysis. The description of the ictal event of the remaining cats was based on the owners' reports. Six of the 9 cats referred to the Institute were in status epilepticus, and 3 had clusters of partial seizures at the time of admission. Cats were in lateral recumbency, had complete loss of consciousness, and showed tonic-clonic motor activity, sometimes changing into uncontrolled jerking movements of the limbs, rhythmic tremors of the whole body, and running motions of the limbs. The ictal event in the remaining cats with generalized seizures was characterized by gradual loss of balance, collapse, and loss of consciousness. These events were accompanied by generalized tonic-clonic motor activity, which started in the pelvic limbs. Subsequently, the cats showed autonomic dysfunction, including salivation, urination, and defecation. In a few cats, the ictal event appeared to be less severe and was characterized by mild generalized muscle spasms of the head and neck, followed by hyperextension of the limbs in lateral recumbency and impaired consciousness. Cats with partial seizures were de-

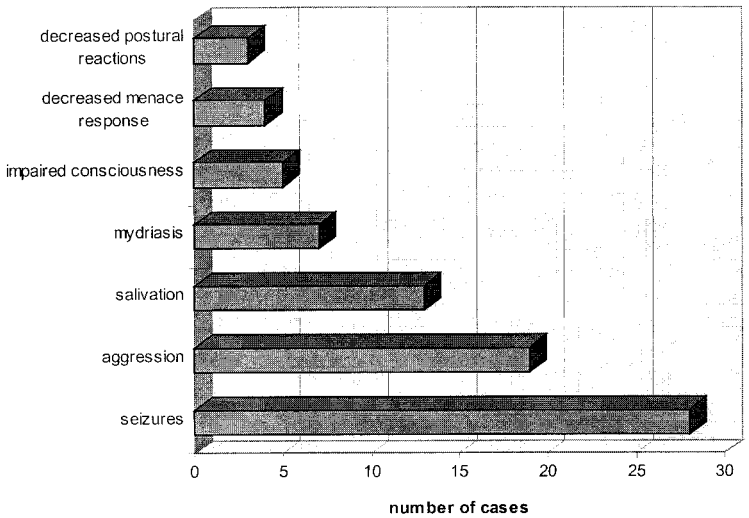

Fig 2. Neurologic signs in cats with hippocampal necrosis.

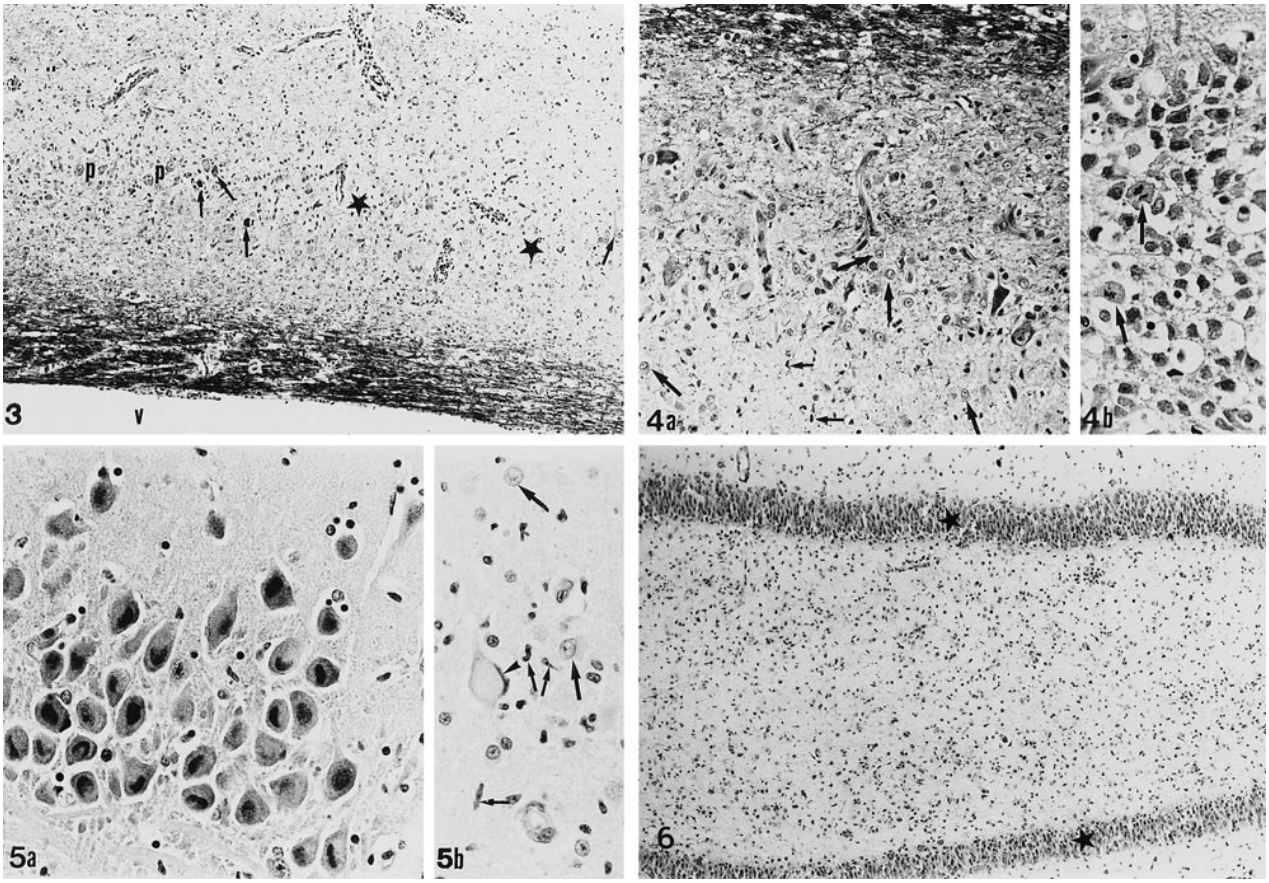

Fig 3. Cat brain. Severe degeneration (arrows) and loss of large pyramidal cells (asterisk), capillary proliferation, and mild perivascular infiltration with lymphocytes and histiocytes. p = preserved neurons; a = alveus; v = ventricle. Luxol fast blue/cresyl violet, 10×.

Fig 4. Cat brain. **(a)** Degeneration and loss of pyramidal cells, gliosis with astrocytes (arrows) and microglia (small arrows), and capillary proliferation with swollen endothelial nuclei. a = alveus. Luxol fast blue/cresyl echt violet, 25×. **(b)** Dentate gyrus with severe shrinkage, nuclear alterations, perineuronal halo, and 2 bizarre mitotic figures (arrows). HE, 40×.

Fig 5. Cat brain. **(a)** Large shrunken pyramidal cells, severe nuclear pyknosis. 40×. **(b)** Neuron with central chromatolysis, pyknotic marginal nucleus (arrowhead), astrocytes (large arrows), and microglia (small arrows). HE, 40×.

Fig 6. Cat brain. Complete loss of pyramidal cells, severe gliosis. The dentate gyrus (asterisk) is unaltered. HE, 10×.

scribed as having muscle twitching of the head, ears, and neck followed by circling, salivation, and behavioral changes, and all had impaired consciousness. During the postictal phase, behavioral changes such as disorientation, hyperexcitability, fear, aggression, jerking, uncontrolled biting, restlessness, ataxia of the pelvic limbs, and central blindness were observed and lasted for a few minutes to hours.

Laboratory Findings

The results of laboratory tests disclosed no abnormalities except increased blood urea nitrogen in 1 cat (114 mg/dL; normal range, 18–34 mg/dL) and abnormal creatine kinase activity in another case (5,140 IU/L; normal range, 0–132 IU/L) . FeLV and FIV tests were negative. CSF analysis was normal in all cats tested. Metaldehyde could not be demonstrated in any of the 10 cats examined toxicologically.

Pathology

General necropsy was unremarkable, and in most cats no gross lesions were visible in the CNS. In a few cats, the areas of the hippocampus and the piriform lobe were bilaterally discolored and softened or had a tendency to crumble.

Histologically, the pathologic changes were restricted to the hippocampus, and in some cats the piriform lobe also was involved. Different features could be distinguished, presumably depending on the duration of clinical disease. Mainly, the large pyramidal neurons of the hippocampus (Fig 4a) and to a lesser extent the small neurons of the dentate gyrus (Fig 4b) and piriform lobe showed different degrees of degeneration (Fig 5) up to total nerve cell loss (Fig 6). In most cats, the neurons were shrunken and contained brightly eosinophilic cytoplasm and pyknotic or lytic nuclei (Fig 5a). Less often, there was central chromatolysis with eccentric pyknotic nuclei (Fig 5b). In most cats, capillary proliferation with swollen endothelial nuclei was present and paralleled the severity of the neuronal necrosis. Occasionally, blood vessels showed moderate to marked infiltration with lymphocytes and histiocytes (Figs 3, 7). In all cats, microgliosis and astrocytosis were prominent (Fig

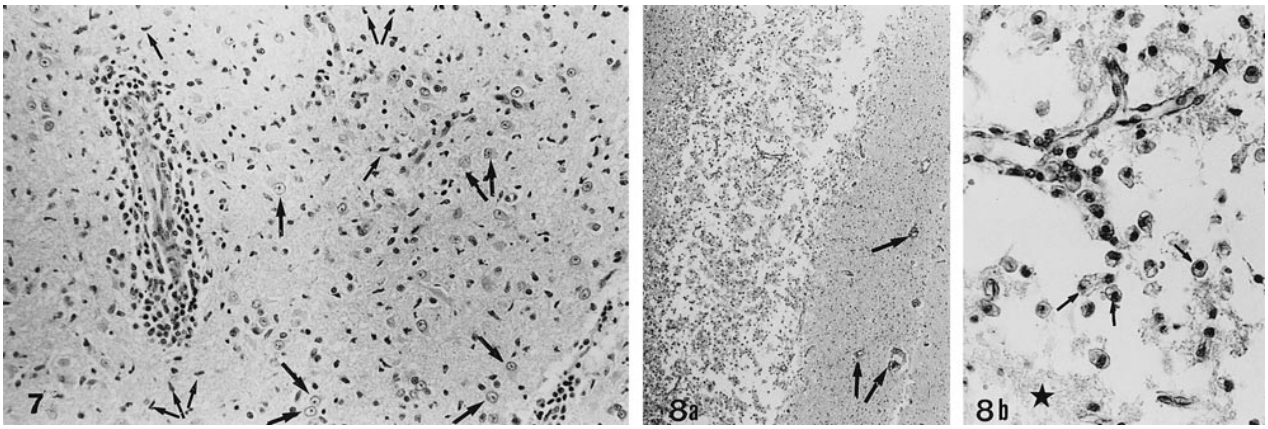

Fig 7. Cat brain. Area with complete loss of pyramidal cells and gliosis, astrocytes (large arrows), microglia (small arrows), capillary proliferation, and lymphohistiocytic perivascular infiltration. HE, 25×.

Fig 8. Cat brain. **(a)** Complete disintegration of pyramidal cell layer. Mild perivascular infiltration (arrows). HE, 10×. **(b)** Proliferated capillary with swollen endothelial nuclei, neuropil debris (asterisk), and macrophages (arrows). HE, 40×.

6). In cats with a longer clinical course and complete or almost complete loss of neurons (Fig 6), fibrillary astrocytes were numerous (Fig 7). In the most severely affected cats, in which necrosis was detected grossly at necropsy, capillary proliferation formed a network in the meshes of which macrophages and neuropil debris and occasional glial cells were present (Fig 8). Atypical mitotic figures were seen in some necrotic hippocampal areas (Fig 4b).

Discussion

In the present study, the clinical records of 38 cats affected by hippocampal necrosis, sometimes with involvement of the piriform lobe, were evaluated retrospectively. The most striking clinical abnormalities in these cats were seizures.

There still is debate whether or not IE occurs in cats. Although some authors reported that IE occurred in 60% of 42 cats, they did not provide information about the results of neurologic examinations, CSF analysis, brain imaging, and other diagnostic procedures.[7] Other investigators reported a prevalence of IE as high as 7% in cats.[8] In contrast, several authors have considered seizures in cats as almost invariably being the result of structural brain disease and indicated that IE is very rare in this species.[9–12] Generalized or atypical complex-partial seizures in cats often are mild and therefore not easily recognized as such by the owner, especially at the beginning of the disease.[9,14] Nevertheless, as a result of video recordings and detailed descriptions from owners, we were able to define the clinical characteristics of the seizures in the study cats. Most of the seizures were generalized, were peracute in onset, and had a tendency to quickly worsen to severe clusters with tonic-clonic motor activity and to status epilepticus in some cats. Despite precise descriptions, it was not always possible to determine whether these events were primary or secondary generalized seizures. A similar progressive clinical course also was observed in cats with complex-partial seizures. Partial or high-frequency seizures seem to be a good clinical indicator for structural brain diseases,[9,15–17] and the study cats were classified in the category of symptomatic epilepsy rather than IE. In addition, interictal neurologic deficits, which are a hallmark of symptomatic epilepsy, were present in most of the cats and consisted mainly of behavioral changes such as aggression, fear, hyperexcitability, chasing, and uncontrolled biting. These signs are consistent with a forebrain disorder, in particular a lesion involving the limbic system. Most of the cats showed an increasing frequency and intensity of the seizures despite treatment. This finding is consistent with the observation that symptomatic epilepsy is less responsive to treatment than is IE and that high-frequency seizures also may indicate structural brain damage.[12] Furthermore, these results confirmed that the duration of epileptiform disorders and especially the cumulative number of seizures seem to correlate well with the development of refractory seizures[10,14] and with a poor prognosis.[11] Because all of the laboratory analyses including CSF examination provided no indication of abnormalities, we postulated a degenerative disease as a possible cause of the neurologic signs.

The most conspicuous pathologic feature of this degenerative CNS disorder was the restriction of bilateral destructive lesions to the hippocampus and the piriform lobe, which are parts of the limbic system. There are some similarities between our findings and FIE, which has been reported in North America and in which severe necrotizing lesions and infarction of the cerebrum are found, also often involving hippocampus and piriform lobe.[18] However, in sharp contrast to the lesions in the study cats, the lesions of FIE often are unilateral or at least assymmetric and not selective. Furthermore, FIE tends to resolve spontaneously, with total or partial recovery, depending upon the extent of the brain damage, although permanent behavioral changes or seizures may be a cause for euthanasia.[2,3]

Bilateral symmetrical degenerative lesions with an acute onset are typical for metabolic or toxic disorders. A major finding was neuronal damage morphologically classified as ischemic necrosis.[19] This neuronal lesion has been associated with excitotoxicity, especially in the hippocampus, which is rich in *N*-methyl-D-aspartate (NMDA) receptors. Overstimulation of cells by excitotoxic amino acids may

lead to cell damage. This mechanism of cell death is important in ischemia. In humans, the hippocampus is extremely and selectively vulnerable to damage by ischemia.[19] This neuronal lesion also can result from other excitotoxic events, such as poisonings with glutamate or kanaic acid or other compounds interacting with NMDA receptors. No evidence was found for an underlying cardiovascular disorder in these cats, and it is unlikely that the lesions resulted from global ischemia. As reviewed by Summers et al,[20] lesions of the ischemic type in these areas, especially the hippocampus, also have been thought to be sequelae rather than the structural cause of severe seizures, including status epilepticus. This explanation appears to hold for humans, but the question of to what extent seizure-induced lesions occur in domestic animals has not been resolved. The fact that no neuronal damage is found in most animals that are euthanized because of severe seizures whereas all cats in the present series showed severe pathology argues against the hypothesis that the lesions were the result of idiopathic seizures. Although the possibility cannot be excluded that the severe seizures observed in these cats may have contributed to further neuronal destruction of the ischemic type, neurons with severe central chromatolysis, which were seen in several cats, suggest a pathomechanism other than seizure-induced excitotoxicity. In addition, the observation that 2 small clusters of 2 and 4 animals, respectively, from the same areas developed signs at around the same time is suggestive of an environmental and probably toxic cause. Selective degeneration of the hippocampus and piriform cortex has been described in dogs that have received halogenated quinoxaline compounds, formerly used in human medicine to treat diarrhea.[21] Erroneous administration of such a compound could not be determined from the history in any of the 38 cats in this study. These drugs were withdrawn from the market because of adverse effects in humans before the 1st seizure cases in this series of cats occurred.

Because of the uniform clinical and neuropathologic features, the cases presented here appear to constitute a disease entity. Further prospective epidemiologic and toxicologic studies are necessary to elucidate the cause of feline hippocampal necrosis.

Footnotes

[a] Klüver-Barrera, Merck, Zurich, Switzerland
[b] Holmes, Merck, Zurich, Switzerland

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