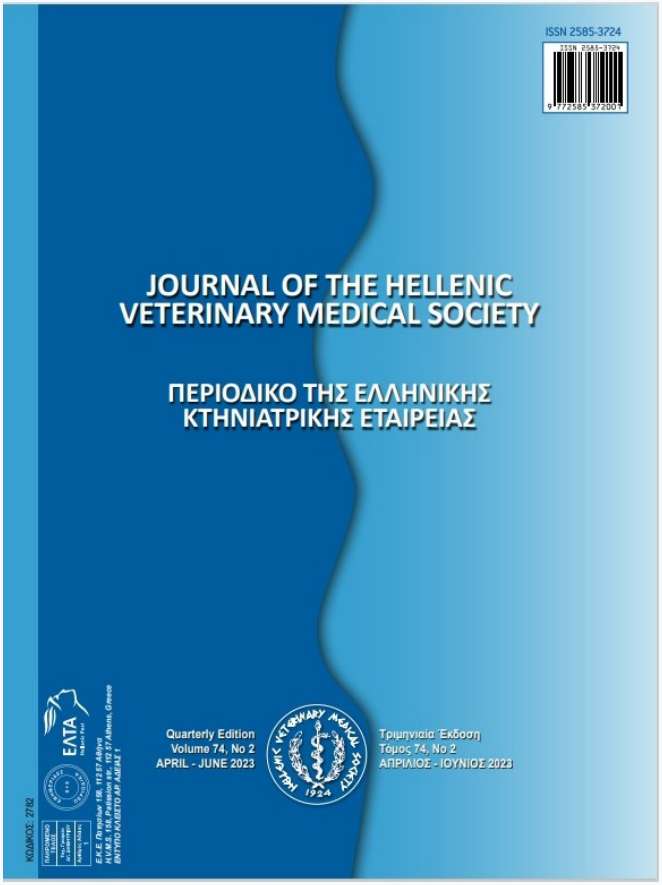
Journal of the Hellenic Veterinary Medical Society

Vol 74, No 2 (2023)



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doi: 10.12681/jhvms.27048

To cite this article:

Yun, T., Koo, Y., Chae, Y., Lee, D., Park, J., Son, M., Kim, H., Yang, M., & Kang, B. (2023). Long-term observations of feline meningoencephalitis of unknown etiology: clinical, CSF, and MRI findings. *Journal of the Hellenic Veterinary Medical Society*, *74*(2), 5869–5872. https://doi.org/10.12681/jhvms.27048

J HELLENIC VET MED SOC 2023, 74 (2): 5869-5872
ΠΕΚΕ 2023, 74 (2): 5869-5872

Case report
Κλινικό περιστατικό

Long-term observations of feline meningoencephalitis of unknown etiology: clinical, CSF, and MRI findings

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ABSTRACT: A 4-year-old female, neutered Turkish Angora cat presented with acute onset of obtundation, right-sided head turn, and rolling. Postural reactions were either absent or decreased in all four limbs. Cranial nerve examination (menace response, pupillary light, and oculocephalic reflex) were absent or decreased. Magnetic resonance imaging (MRI) demonstrated demarcated lesions in the thalamus and brainstem, which were marked hyperintense on T2-weighted and fluid-attenuated inversion recovery images and isointense on T1-weighted images. Cerebrospinal fluid (CSF) nucleated cell count was markedly elevated (258 cells/μl) with a neutrophilic pattern. The CSF polymerase chain reaction for infectious agents was negative. Feline meningoencephalitis of unknown etiology (FMUE) was the most promiment diagnosis. The cat underwent prednisolone monotherapy (3 mg/kg, twice daily), gradually tapered off. Follow-up clinical signs, MRI, and CSF analysis were performed at 33, 118, and 611 days after the initial therapy. At 33rd days, abnormalities of clinical signs, MRI, and CSF had almost disappeared. At 139th days, since all examinations showed normal findings, treatment stopped. At 611th days, the final examinations showed no remarkable findings. This is the first case describing changes in the clinical signs, MRI findings, and CSF analysis of FMUE with long-term follow-up.

***Keywords*:** Cat, long-term, meningoencephalitis, non-infectious.

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Date of initial submission: 16-5-2021
Date of acceptance: 16-12-2021

INTRODUCTION

Central nervous system (CNS) diseases with inflammatory etiology are one of the most common types of neurologic diseases in veterinary medicine (Bradshaw et al., 2004; Fluehmann et al., 2006). Meningoencephalitis or meningoencephalomyelitis of unknown etiology (MUE) is a representative CNS inflammatory disease with no identifiable infectious agent in dogs. However, in cats, one of the most significant inflammatory diseases is pyogranulomatous meningoencephalitis caused by infection with feline infectious peritonitis virus (Bradshaw et al., 2004). While canine MUE has been presently well-described, only a few studies regarding CNS non-infectious inflammatory disease in cats, feline MUE (FMUE), have been reported (Künzel et al., 2017; Negrin et al., 2017; Nessler et al., 2020). Antemortem diagnosis of FMUE can be challenging. However, a diagnosis of FMUE could be tentatively obtained by magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis. Treatment of FMUE generally depends on glucocorticoid-based therapy with symptomatic care (Negrin et al., 2017). This is the first report describing a case of FMUE with long-term observation, providing clinical, CSF, and MRI findings.

CASE HISTORY

A 4-year-old female, neutered Turkish Angora cat presented with acute onset of rolling to the right direction and a right head tilt, lasting for 24 hours. On admission, physical examination was unremarkable except for tachypnea (60 breaths/min). Neurologic examination findings included obtunded mental status, miosis bilaterally, and delayed direct and consensual pupillary light reflexes. The result of complete blood count was normal; biochemistry profile showed mildly increased aspartate aminotransferase (AST, 164 IU/L; reference range, 6−44 IU/L) and severely increased creatine kinase (CK, 39,890 IU/L; reference range, 49−688 IU/L). Based on the clinical signs and neurologic examinations, a multi-focal disease was suspected, and neuroanatomical localization of the lesions was the right forebrain and brainstem.

Brain MRI was performed using a 0.3 Tesla unit (Airis II, Hitachi, Japan). The lesion was identified in the thalamus and brainstem; it was hyperintense in T2−weighted (Figure 1A and 1D), fluid-attenuated inversion recovery (FLAIR) (Figure 1B) images, as well as isointense in T1−weighted images (Figure 1C). Postcontrast images were also acquired, and no contrast enhancement was observed. CSF cytological examination revealed intact neutrophilic pleocytosis (total nucleated cell count, 258 cells/μL; reference range<5 cells/μL; neutrophils 80%, lymphocytes 11%, and monocytes 9%); no microorganisms were detected. CSF total protein concentration was in the upper reference range (0.3 g/L; reference range ≤0.3 g/L). CSF polymerase chain reaction (PCR) results for infectious agents (Feline coronavirus, *Bartonella* spp., *Cryptococcus* spp., and *Toxoplasma gondii*) were negative. Based on history, signalment, and clinical assessments, FMUE was strongly suspected.

The cat was treated with immunosuppressive dosage of prednisolone (3 mg/kg, twice daily, SC; Solon®, Handong, Seoul, South Korea). Five days after the commencement of the immunosuppressive therapy, all neurologic signs except for severe head tilt had improved, and the cat was discharged. The dose of prednisolone was tapered to 2 mg/kg twice daily. Nineteen days after the commencement of immunosuppressive therapy, head tilt, which was the only neurological symptom, had further improved, and the dose of prednisolone was tapered off to 1.5 mg/kg twice daily. Thirty-three days post-immunosuppressive therapy, a second MRI was performed to evaluate therapeutic effectiveness, and most lesions were not observed (Figure 1E−1H). CSF analysis was normal. Therefore, the dose of prednisolone was reduced to 1 mg/kg twice daily. From 33 to 118 days, the neurological signs did not deteriorate and the dose of prednisolone was reduced using the following protocol: 1.0 mg/kg q12h for 4 weeks; 0.5 mg/kg q12h for 4 weeks; 0.5 mg/kg q24h for 4 weeks. On 118 days post-immunosuppressive therapy, a third MRI and CSF analysis were performed with no remarkable finding (Figure 1I−1L). Therefore, the dose of prednisolone was tapered off to 0.5 mg/kg every other day, and the treatment was discontinued after a total of 139 days. The head tilt persisted 472 days after the end of treatment and the cat was clinically normal. Brain MRI and CSF analysis were performed 611 days post-immunosuppressive therapy, and no abnormal findings were revealed (Figure 1M−1P).

DISCUSSION

We described the first case of FMUE with long-term observation, including clinical, MRI, and CSF findings. The cat showed recovery with prednisolone monotherapy, showing complete remission of clinical, MRI, and CSF findings for 611 days.

Inflammatory encephalopathies are the most recognized neurologic CNS diseases in cats. The most common disorder is feline infectious peritonitis (51%), followed by a non-infectious encephalitis or meningitis (35%) (Bradshaw et al., 2004). One study about feline inflammatory CSF analysis reported that 63% of the cats were presumptively diagnosed, and

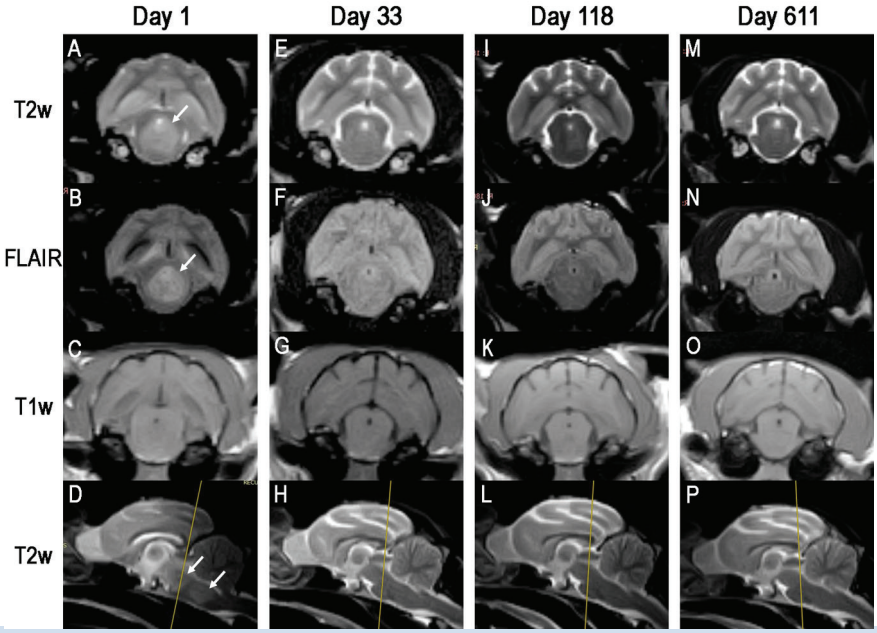

Figure 1. Serial magnetic resonance imaging (MRI) characteristics of feline meningoencephalitis of unknown etiology (FMUE). (A−D) The first MRI acquired on day 1. Demarcated lesions (arrows) of the midbrain, pons, and medulla oblongata were identified as hyperintense in T2−weighted (T2w), fluid attenuated inversion recovery (FLAIR) images and isointense in T1−weighted image (T1w). The second (E–H), third (I–L), and fourth (M–P) MRI were acquired at 33, 118, and 611 days after the initial therapy, respectively. The intracranial lesions observed in the first MRI were no longer identified.

a specific diagnosis was not obtained in 37% of the cats (Singh et al., 2005). In the present case, results of the CSF analysis revealed neutrophilic pleocytosis (80%) and moderately increased total nucleated cell count (258 cells/μL) with the upper reference value of protein concentration (0.3 g/L). Typically, CSF analysis of FMUEs shows pleocytosis and elevated protein concentration (Negrin et al., 2017). Various types of pleocytosis were reported; mixed, lymphocytic, mononuclear, neutrophilic, and eosinophilic pleocytosis were 31.3%, 31.3%, 18.8%, 12.5%, and 6.3%, respectively (Negrin et al., 2017). Total nucleated cell count is mildly to moderately elevated (75%, 5–80 cells/μL; 25%, 81–500 cells/μL) in FMUE (Negrin et al., 2017). Mildly elevated protein concentration (median, 0.5 g/L; range, 0.21– 22.25 g/L) was identified in 75% of FMUE (Negrin et al., 2017).

While the treatment protocol of canine MUE has been well-described, there were few reports of treatment methods for FMUE (Singh et al., 2005; Negrin et al., 2017; Nessler et al., 2020). However, corticosteroid-based therapy is commonly used for the treatment of FMUE. One retrospective study of suspected FMUE used dexamethasone alone; dexamethasone followed by prednisolone; or prednisolone with an immunosuppressive dose (1mg/kg, twice daily, PO) (Negrin et al., 2017). Two successfully recovered cats underwent prednisolone therapy (Singh et al., 2005). Other immunomodulatory medications, including cytosine arabinoside and lomustine, were also used (Negrin et al., 2017). Another study of FMUE, confirmed with histopathology, could not show a successful treatment method due to euthanasia despite anti-inflammatory treatment (Nessler et al., 2020).

There have been no meaningful statistical data of median survival time available due to rapid euthanasia or lack of follow-up after discharge (Singh et al., 2005; Negrin et al., 2017; Nessler et al., 2020). Although some cats were revealed to be steroid-responsive with a complete remission for up to 15 months, details of clinical signs, diagnostic findings, and therapeutic responses were not described (Singh et al., 2005; Negrin et al., 2017).

Creatine kinase (CK) is an enzyme that catalyzes the conversion of creatine to make phosphocreatine and adenosine diphosphate using adenosine triphosphate (Foreback and Chu, 1981). Three isoenzymes of CK have been identified: skeletal muscle, myocardium, and brain (Foreback and Chu, 1981). CK is generally elevated in muscle damage caused by acute muscle injury or chronic disease. The most common causes of increased CK activity in cats are infectious diseases, renal failure, and non-infectious inflammatory diseases (Aroch et al., 2010). The highest value of CK activity in cats was reported in arterial thromboembolism from cardiomyopathy (506,870 IU/L), and the highest median value of CK activity was reported

in sepsis (14,062 IU/L; range, 278−97,829 IU/L) and high-rise syndrome (12,450 IU/L; range, 435−32,920 IU/L) (Aroch et al., 2010). In canine neurologic disorders, such as degenerative, inflammatory, space-occupying diseases and idiopathic epilepsy, many CK isoenzymes are elevated (Paltrinieri et al., 2017). In feline neurologic diseases, the median CK activity was 569 IU/L (range, 71−12,106 IU/L) (Aroch et al., 2010). In the present case, there were no remarkable findings of cardiomyopathy, infectious disease, renal failure, and high-rise syndrome (broken bone, injuries to the legs, and internal injuries), therefore, severe elevation of CK concentration seemed to originate from muscle damage caused by severe rolling, prolonged recumbency, and neuronal injuries.

The limitation of this case is that a biopsy was not performed for definitive diagnosis. Moreover, PCR analysis was partially performed for infectious agents; bornavirus, feline leukemia virus, feline herpesvirus, *Leishmania infantum*, feline calicivirus, feline parvovirus (panleukopenia virus), and feline immunodeficiency virus were not completely ruled out. However, the cat seemed to not have had any infectious diseases because there were no remarkable systemic (ocular, nasal, cutaneous signs, etc.), and hematologic (non-regenerative anemia, increased serum globulin concentration, panleukopenia, etc.) findings related to the above mentioned viral and parasitic diseases. Among infectious intracranial diseases, the incidence of bacterial meningoencephalitis is 1% and 3.7% in cats with neurologic disorders and inflammatory CNS disorders, respectively (Rand et al., 1994; Bradshaw et al., 2004).The prognosis for feline bacterial meningoencephalitis is poor and 60% of cats with bacterial meningoencephalitis were euthanized or died due to clinical deterioration (Balk et al., 1974; Sims, 1974; Stowater et al., 1978; Dow et al., 1988; Kraus et al., 1989; Klopp et al., 2000; Blauvelt et al., 2002; Cook et al., 2003). In the present case, the cat had no other signs of bacterial infection (systemic signs including respiratory, gastrointestinal symptoms, and pyrexia, neutrophilia with a left shift, neck pain, etc.). Moreover, there was no evidence of direct spread from the nasal cavity, ears, eyes, and hematogenous extension (bacterial endocarditis, hepatic abscess, pneumonia). Furthermore, despite the immunosuppressive dosage of glucocorticoids, which is contraindicated in infectious disease, the neurologic signs were resolved completely rather than deteriorated. Based on the evidence coming from the results and the long-term follow-up, the diagnosis of FMUE was established excluding infectious meningoencephalitis.

This is the first reported case showing the consecutive alterations in the MRI, CSF, and clinical findings of a steroid-responsive FMUE over a long period (611 days), providing useful information for the future.

ACKNOWLEDGEMENTS

The authors thank Seojin Park for valuable assistance and care of the cat included in the case report. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2021R1A2C1012058) and Basic Science Research Program through the NRF funded by the Ministry of Education (2022R1I1A1A01069972).

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