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[i]Neuropathological and Molecular Study of FIP, FIV, and FeLV in the Central Nervous System of Twenty Cats

Shahab Ramezanpour Eshkevari[1], Farhang Sasani[1], Sara Shokrpoor[1], Seyed Hossein Mardjanmehr[1], Hesameddin Akbarein[2], Iradj Ashrafi Tamai[3]

1- Department of Veterinay Pathology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran.

2- Department of Food Hygiene and Quality Control, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran.

3-Department of Microbiology and Immunology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran

ABSTRACT

Background: Neurological conditions constitute approximately 10% of the total feline cases referred to veterinary clinics. Such cases often present various manifestations of central nervous system (CNS) damage, including inflammatory lesions, neoplastic growth, structural and cellular transformations.

Objectives: The main aim of this study to identify histopathological changes in the CNS of cats that had succumbed to neurological symptoms.

Methods: Microscopic evaluation of different sections within the CNS was conducted on 20 cats that had either died naturally or were euthanized due to neurological signs. After performing necropsy, we examined the CNS tissues and conducted PCR testing to screen for possible viral infections, including feline infectious peritonitis (FIP), feline Immunodeficiency virus (FIV), and feline leukemia virus (FeLV).

Results: The majority of cases showed characteristic histopathologic lesions, notably mononuclear and suppurative meningoencephalitis, perivascular cuffing, disseminated intravascular coagulation, granulomatous meningoencephalitis, acute neuronal necrosis, liquefactive necrosis, ependymitis, thrombosis, and demyelination. Among the 20 cats studied, 12 tested positive for FIP by PCR analysis, while 5 cats exhibited positive results for FIV. FeLV PCR tests displayed positive results in 4 cats. no evidence of Feline Spongiform Encephalopathy (FSE) was observed in any of the cases.

Conclusions: This study is the first of its kind conducted in Iran. Based on the results, the most prevalent viral agents infecting the central nervous system in cats were identified as FIP, FIV, and FeLV, respectively. The investigation did not reveal any evidence of FSE in cats with neurological signs.

Keywords: CNS, Feline, Histopathology, Necropsy, PCR

1. Introduction

The nervous system of cats can be influenced by various factors, leading to the occurrence of neurological diseases, which are frequently observed in this species. It's worth noting that clinical cases related to neurology make up around 10% of the total case load in feline medicine referral clinics (Gunn-Moore, 2005). Furthermore the central nervous system in cats can be prone to bacterial infections caused by a diverse range of pathogens, including *Escherichia coli*, *Klebsiella spp.*, *Pasteurella spp.*, *Mycobacteria*, *Bacteroides spp.*, and *Fusobacterium spp.*(Hertzsch & Richter, 2022). *Chlamydia felis* is an important agent with zoonotic susceptibility often isolated from cats with chronic conjunctivitis (Barimani *et al*., 2019).

Additionally, neurological diseases in cats are attributed to various viral agents, which include Feline coronavirus (FCoV), Feline panleukopenia virus (FPV), Feline immunodeficiency virus (FIV), Feline leukemia virus (FeLV), Rabies virus, Aujeszky's disease virus, Feline herpesvirus-1 (FHV1). Mycotic infections affecting the central nervous system (CNS) of cats are infrequent; nevertheless, when such infections do occur, they can lead to severe illness. Pathologically, fungal diseases in the CNS are characterized by manifestations such as meningoencephalomyelitis, sinonasal lesions, ventriculitis, and CNS granuloma (Bentley *et al*., 2018). *Feline infectious peritonitis* (FIP) is a viral disease of cats caused by certain strains of a virus called the feline coronavirus which is different from the human coronavirus. Covid-19 can be transmitted from humans to cats (Mohebali *et al*., 2022). Feline Infectious Peritonitis is a deadly disease that poses a significant threat to domestic and wild felids worldwide. The causative agent is the feline coronavirus (FCoV), which exists in two pathotypes: feline enteric coronavirus (FECV) and feline infectious peritonitis virus (FIP) (Felten & Hartmann, 2019). The viral genomic mutation that cause changes in cellular tropism can affect the virulence and development FIP (Kennedy, 2020). FCoV strains are subdivided into two distinct biotypes: Feline Enteric Coronavirus and Feline Infectious Peritonitis virus (FIPV). Serotype 1 FCoV includes unique feline strains, while serotype 2 appears to have arisen from the recombination

between type 1 FCoV and canine coronavirus (Farsijani *et al*., 2023). FIP is characterized by localized or disseminated fibrinous lesions accompanied by pyogranulomatous and granulomatous inflammation, often leading to proteinaceous effusions in blood vessels. Typical signs of FIP include granulomatous or necrotizing phlebitis and, in some cases, periphlebitis (Malbon *et al*., 2020). Furthermore, lesions in the CNS are frequently observed, with primary impacts on the leptomeninges, ventricles, choroid plexus, and occasionally the neuroparenchyma (Wang *et al*., 2018). A prion is an infectious agent responsible for a group of lethal and neurodegenerative diseases (Kathiriya *et al*., 2020). Feline spongiform encephalopathy (FSE) is a transmissible spongiform encephalopathy that arises from the ingestion of feed contaminated with tissue from cattle affected by bovine spongiform encephalopathy (BSE). It is characterized by the accumulation of an abnormal isoform of the prion protein in the central nervous system (Iulini *et al*., 2008). Parasitic diseases that can infect the central nervous system in cats include Toxoplasmosis, Cuterebra larvae myiasis, *Toxocara Spp*. visceral larva migrans, Sarcocystis, and *Dirofilaria immitis* (Gunn-Moore, 2005). *Toxoplasma gondii* infects all species of warm-blooded animals, including humans, and domestic cats and other felidae are its definitive hosts (Mosallanejad et al., 2017)

Additionally persisting pain also may lead to chronic diseases and cause some changes in the central nervous system (Nikjooy *et al*., 2022). This study represents the initial investigation in Iran, where histopathological examination was conducted on central nervous system lesions in displaying neurological symptoms. Moreover, an assessment of the central nervous system tissue was performed to detect the presence of feline spongiform encephalopathy.

2. Materials and Methods

This study was designed to explore feline neurological cases, involving necropsy investigations of cats that had succumbed to several neurological disorders. A standard post-mortem protocol was adhered to, encompassing gross examination, histopathological analysis, and PCR tests for viral infections like FIV, FeLV, and FIP. A total of 20 cats, displaying neurological signs or euthanized due to unresponsiveness to treatment or poor prognosis, were subjected to necropsy

after recording their medical history and clinical manifestations. The cases were referred from private sector veterinary centers located in Tehran city and Tehran University Veterinary Hospital and were necropsied in the Pathology Department of the Faculty of Veterinary Medicine of Tehran University. During the necropsy process, the brain and spinal cord of each animal were completely removed immediately after death (Fig. 2).

Histopathological Investigations

Histopathological sampling was performed from various anatomical regions of the central nervous system, including the cerebral cortex, cortical and basal parts of the cerebellum, hippocampus, thalamus, posterior and anterior sections of the medulla oblongata, as well as different segments of the spinal cord, such as cervical, thoracic, lumbar, and sacral regions (Iulini *et al*., 2008). Tissues were placed in a 10% neutral buffered formalin solution to maintain their structural integrity. After tissue process, Hematoxylin and Eosin (H&E) staining were applied to the prepared slides. The sections were then mounted onto glass slides, ready for detailed histopathological analysis (Slaoui & Fiette, 2011).

Special Staining

In specific cases where the destruction of the myelin structure was detected, a targeted Luxol Fast Blue staining technique was applied to the tissues (Meknatkhah *et al*., 2019). Immunohistochemical staining with the CD163 marker was used on histopathological sections because of its immunoreactivity can be observed in resident macrophages and using CD68 marker to detect inflammatory macrophages (Lau *et al*., 2004). The purpose of this staining was to distinguish and differentiate inflammatory and tissue macrophage cells from other cell types (Hirabayashi *et al*., 2020).

Molecular Diagnostic (PCR) Testing

Tissue samples from a small piece of the different areas of the brain and spinal cord that were mentioned in the pathology sampling, were collected using a sterile scalpel blade and after

labeling, were stored at a temperature of -20 degrees Celsius. SinaClon kit was used for RNA extraction. In this step, Sina Clon cDNA synthesis kit (Cat. No: RT5201), sterile and nuclease-free micro-tubes were used. Synthesized cDNA was used to perform RT PCR process to detect FIV, FeLV, and FIP viruses (Najafi *et al*., 2014).

Statistical Analysis

The statistical analyses were performed using SPSS software version 26.0. Descriptive statistics were presented as Mean ± Standard Error of the Mean (SEM) and Median. To determine statistical significances, Chi-square and Fisher's Exact tests were employed. A p-value less than 0.05 was considered statistically significant (SPSS Inc., Chicago, IL).

3.Results

In this study, 20 cats that died due to neurological symptoms were investigated. The average age was 2 years, with 18 being of mixed breed and 2 of Scottish breed. Gender distribution included 7 intact females, 1 spayed female, 10 intact males, and 2 castrated males. Common neurological symptoms observed were ataxia, incoordination, head tilt, proprioceptive deficits, and tremors. Histopathologic lesions were detected in all CNS samples. The lesions were associated with various neurologic diseases, and in descending order of frequency, they were categorized as follows: meningitis (Fig.4, a, b, c, h, and p), meningoencephalitis (Fig.4, h and p), granulomatous inflammation (Fig.4, a, o, and r), nonsuppurative encephalitis (Fig.4, d, c, and p), suppurative encephalitis (Fig.4, i), and hemorrhage (Fig.4, q). Notably, no histopathologic lesions of Feline Spongiform Encephalopathy were detected in any of the cats. Other notable histopathological findings included perivascular cuffing (PVC) (Fig.4, d, e, f, o, and p), disseminated intravascular coagulation (DIC) (Fig.4, d), edema, thrombosis (Fig.4, b), demyelination (Fig.4, m and n), acute neuronal death (Fig.4, j and k), gliosis, and the presence of bacterial colonies (Fig.4, g). Based on the PCR results performed on brain tissue samples, the findings revealed that 12 cats tested positive for FIP, while 5 cats were infected with FIV, and 4 cats were diagnosed with FeLV

disease (Fig. 3). The PCR result of FIP disease was positive in all the cases that had granulomatous inflammation in the central nervous system but Fisher's exact test showed no statistically significant difference between the presence of general injuries of the nervous system such as PVC, encephalitis, DIC, perivascular edema, acute neuronal necrosis, liquefactive necrosis, ependymitis, thrombosis, demyelination, CD163, satelitosis and gliosis with FIP, FIV and FeLV positivity (P >0.05).

4. Discussion

The manifestations of nervous signs in cats can be similar across different diseases that affect the nervous system. This similarity in clinical presentation poses a challenge in diagnosing specific neurological conditions only based on clinical signs. Therefore, histopathological investigation of the CNS, as focused in this study, becomes critical in recognizing the underlying pathology and causative factors, such as viral diseases like FIV, FeLV, and FIP. This evaluation aids in distinguishing between different neurological disorders and develops our understanding of their typical features, finally leading to better management and treatment approaches for affected feline patients(Camps *et al*., 2019). Diseases that affect the central nervous system in cats include Inflammatory, degenerative, congenital and feline spongiform encephalopathy (FSE) (Bradshaw *et al*., 2004). Central nervous system infection can be caused by wide range of pathogens including bacterial agents, viruses, fungi, parasites, and prions. Infection in the central nervous system is mainly seen in the form of meningitis, encephalitis and abscess (Giovane & Lavender, 2018). In this current study, beside the histopathological analysis of brain and spinal cord tissues, molecular evaluation was performed to screen viral diseases. Among the detected neurologic lesions, the most prevalent were characterized as inflammatory lesions, including meningitis, encephalitis, and meningoencephalitis. These inflammatory lesions displayed mononuclear inflammation, a typical characteristic often associated with viral infections. This inclusive methodology combining histopathological and molecular assessments offers valuable data for understanding the underlying viral etiologies and their impact on the CNS in affected cats (Murillo *et al*., 2022). Further important histopathological findings in CNS tissues included the presence of granulomatous meningoencephalitis, detected at varying

intensities. Alongside these, common histopathological lesions, such as PVC, encephalitis, DIC, perivascular edema, acute neuronal necrosis, liquefactive necrosis, ependymitis, thrombosis, demyelination, satelitosis, and gliosis, were apparent in nearly all cases. Notably, four cats exhibited manifestations of granulomatous inflammation, with positive PCR results for FIP. In certain cases, where infiltration of macrophages was confirmed through immunohistochemical staining with the CD 68 marker, the PCR results also yielded positive results for FIP disease. Study further confirms FIP as the predominant cause of granulomatous inflammation in cats (Gonçalves, 2020). Even though granulomatous lesions were not present in all cats with positive PCR tests for FIP, it is important to know that studies have confirmed the potential for false positives in PCR testing. To reach a definitive diagnosis of pathological lesions associated with FIP disease, additional measures like Immunohistochemistry for FcoV are recommended (Barker & Tasker, 2020). FIV has the ability to attack the CNS by crossing the blood-brain barrier just after primary infection. This invasion occurs through infected leukocytes. Once inside the CNS, FIV exhibits productive cell tropism for microglia and perivascular macrophages (Power, 2018). Non-suppurative meningoencephalitis is a prominent characteristic detected in viral infections like FIV and FeLV. Infiltrations of lymphocytes were evident in various regions of the CNS, including the leptomeninges, neuropil, and particularly in the Virchow-Robin space (Schwab *et al*., 2007). Microscopic examination of the central nervous system in cats affected by viral diseases, such as FIV, reveals notable pathological changes. These changes include perivascular mononuclear cell infiltrations observed within the meninges of the brain, the choroid plexus, and the dura of the spinal cord (Ryan *et al*., 2005). In the present study, the most observed lesions in the central nervous system of cats whose their PCR tests for FIV and/or FeLV were positive, mononuclear meningitis, perivascular cuffing of inflammatory cells mainly lymphocytes and plasma cells that is a hallmark of a viral or immune-mediated inflammatory process were the major histopathological findings (Matiasek *et al*., 2023). Besides the mentioned microscopic lesions, the rate of other detected microscopic findings based on their prevalence included encephalitis, hyperemia, meningeal edema, perivascular edema, acute neuronal necrosis, liquefactive necrosis, and ependymitis, respectively. Moreover, another notable neurological lesion detected was the destruction of the myelin structure. This lesion is encountered in various

neurological diseases. Degeneration of the axon's myelin, along with the loss of neurons and glial cells, ischemia, and inflammation, contributes to the formation of glial scars and cystic cavities in the spinal cord (Khodabakhshi Rad *et al*., 2023). Notably, FSE was a significant disease which monitored in this study, and its examination in Iran was conducted for the first time. FSE has been reported in several countries worldwide in recent years, including Germany, Norway, Great Britain, and France (Bratberg *et al*., 1995; Lezmi *et al*., 2003; Hilbe *et al*., 2009; Eiden *et al*., 2010). FSE is classified as a subtype of transmissible encephalopathy, and it is caused by prions. Because of the similarities between FSE and Bovine Spongiform Encephalopathy (BSE), there are concerns about the possible occurrence of BSE in Felidae (Arnold *et al*., 2017). Because of the similarity of neurological symptoms between FSE and many other neurological disorders in cats, the diagnosis of FSE can be reached through histopathological evaluations, immunohistochemistry, western blot, or ELISA performing on brain. Furthermore, confirmation of the presence of the causative prion responsible for FSE demands the use of molecular diagnostic methods. By combining these approaches, a decisive diagnosis of FSE can be established, allowing accurate differentiation from other neurological conditions (Pearson *et al*., 1992). FSE leads to vacuolation and spongiosis throughout the nervous system, particularly affecting regions such as the medulla oblongata, basal ganglia, and geniculate nucleus (Iulini *et al*., 2008). In this study, which represents the first research on FSE disease monitoring in Iran, no suspected cases of this disease were observed based on the histopathological changes in the nervous system.

5. conclusion

In this study, all cats that exhibited neurological symptoms were found to have microscopic lesions in their CNS tissues. The prevailing viral agents in these cases were FIP, FIV, and FeLV, respectively. Notably, no evidence of FSE was detected in any of cats. These findings shed light on the distinct viral causes behind neurological issues in felines, emphasizing the importance of accurate identification for effective diagnosis and management.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. All animals were examined postmortem and either died of disease or were euthanized due to non-response to treatment with the consent of their owners.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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مطالعه هیستوپاتولوژیک دستگاه عصبی مرکزی در گربه های تلف شده متعاقب بروز علائم عصبی

شهاب رمضانپور اشکوری[1]، فرهنگ ساسانی[1]، سارا شکرپور[1]، سید حسین مرجانمهر[1]، حسام الدین اکبرین[2]، ایرج اشرافی تمای[3]

1. گروه پاتولوژی، دانشکده دامپزشکی دانشگاه تهران، تهران، ایران
2. گروه بهداشت مواد غذایی و کنترل کیفی،دانشکده دامپزشکی ،دانشگاه تهران ، تهران ، ایران
3. گروه میکروبیولوژی، دانشگده دامپزشکی دانشگاه تهران،تهران-ایران.

چکیده فارسی:

زمینه مطالعه: بیماری های عصبی تقریباً 10 درصد از کل موارد گربه سانان مراجعه کننده به کلینیک های دامپزشکی را تشکیل می دهند. چنین مواردی اغلب تظاهرات مختلفی از آسیب سیستم عصبی مرکزی (CNS) از جمله ضایعات التهابی، رشد نئوپلاستیک، دگرگونی‌های ساختاری و سلولی را نشان می‌دهند.
هدف: هدف اصلی شناسایی تغییرات هیستوپاتولوژیک در CNS گربه هایی که در اثر علائم عصبی تلف شده بودند.

روش کار: ارزیابی میکروسکوپی بخش‌های مختلف در CNS بر روی 20 گربه که یا به طور طبیعی مرده بودند یا به دلیل علائم عصبی مورد عمل یوتانایز قرار گرفتند، انجام شد. پس از کالبدگشایی، قسمت های مختلف CNS از نظر هیستوپاتولوژی بررسی گردید و آزمایش PCR به منظور غربالگری عفونت‌های ویروسی احتمالی، از جمله پریتونیت عفونی گربه سانان (FIP)، ویروس نقص ایمنی گربه سانان (FIV) و ویروس لوسمی گربه سانان (FeLV) انجام شد.

نتایج: تغییرات هیستوپاتولوژیک شایع به ترتیب رخداد در گربه ها عبارت بودند از: منتژیت، PVC، انسفالیت، پرخونی، DIC ،ادم منتژ، منتگوانسفالیت گرانولوماتوز، نکروز حاد نورونی، نکروز آبکی، التهاب اپاندیم، ترومبوز و دمیلیناسیون. طبق نتایج به دست امده از PCR بافت سیستم دستگاه عصبی ،12 گربه مبتلا به FIP، 5 گربه مبتلا به FIV و 4 قلاده از گربه ها نیز به FeLV مبتلا بوده اند. در هیچ یک از موارد ضایعات هیستوپاتولوژیک منطبق با بیماری FSE(انسفالیت اسفنجی شکل گربه سانان) مشاهده نشد.

نتیجه گیری نهایی: بر اساس یافته های این مطالعه که برای اولین بار در ایران انجام شد، شایع ترین عوامل ویروسی که سیستم عصبی مرکزی را آلوده می کنند به ترتیب FIP، FIV و FeLV بوده است. یکی از دست آورد ها و نو آوری های مهم در این تحقیق بررسی بیماری FSE بوده است که شواهدی از وقوع آن در بررسی های هیستوپاتولوژی مشاهده نشد.

واژه های کلیدی: دستگاه عصبی مرکزی، کالبدگشایی, گربه، هیستوپاتولوژی، PCR

Table

Table 1. Characteristics of primers used to detect viral diseases

Gene	PCR	Fragment Size (bp)	Primer, Sequence	Reference
FIV	RT-PCR	374	Forward: GAAGAAGGAAATGCAGGTAAGTTTAGAA Reverse: TAATCCT GCTACTGGGTTATACCAATT	(Zhang et al., 2017)
FeLV	RT-PCR	450	Forward: ACTAACCAATCCCCACGC Reverse: ACTAACCAATCCCCACGC	(Victor et al., 2020)
FIP	RT-PCR	223	Forward: GGCAACCCGATGTTTAAAACTGG Reverse: CACTAGATCCAGACGTTAGCTC	(Mohammed Ibrahim et al., 2022)

Figure legends

Figure 1. Anisocoria and uveitis observed in a cat affected by FIP.

Figure 2. Some specimens of the brain and spinal cord extracted from cats following the fixation process.

Figure 3. The electrophoresis results of some PCR products obtained from cats infected with FIP (a), FIV (b), and FeLV (c).

Figure 4. Mononuclear meningoencephalitis of cervical spinal cord in a FIP-positive cat (a), histiocytic cerebral cortex meningitis (b), mononuclear meningitis in which macrophage cells are marked by immunohistochemical staining with CD68 marker (c and d). mononuclear PVC around a blood vessel (arrow head) (d).

Figure 5. non-suppurative encephalitis with remarkable PVC of cerebral cortex (a and b), cerebellar hemorrhage and edema with infiltration of phagocytic Gitter cells (arrows) (c), cerebral histiolymphocytic infiltrate cells include a mixture of macrophages, which are identified by immunohistochemical staining with the CD163 marker (arrows), accompanied by lymphocytes (arrow head).

Figure 6. meningomyelitis with numerous PVC in sacral spinal cord (a), cells mostly consisted of lymphocytes and neutrophils (circle) (b). DIC with presence of bacterial colony (arrow head) in medulla oblongata (c). Demyelination in the basal area of the cerebellum (arrow), Luxol fast blue staining, (d).

Figures

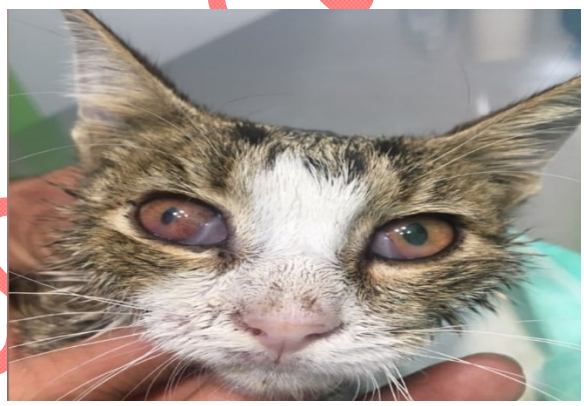

Figure 1.

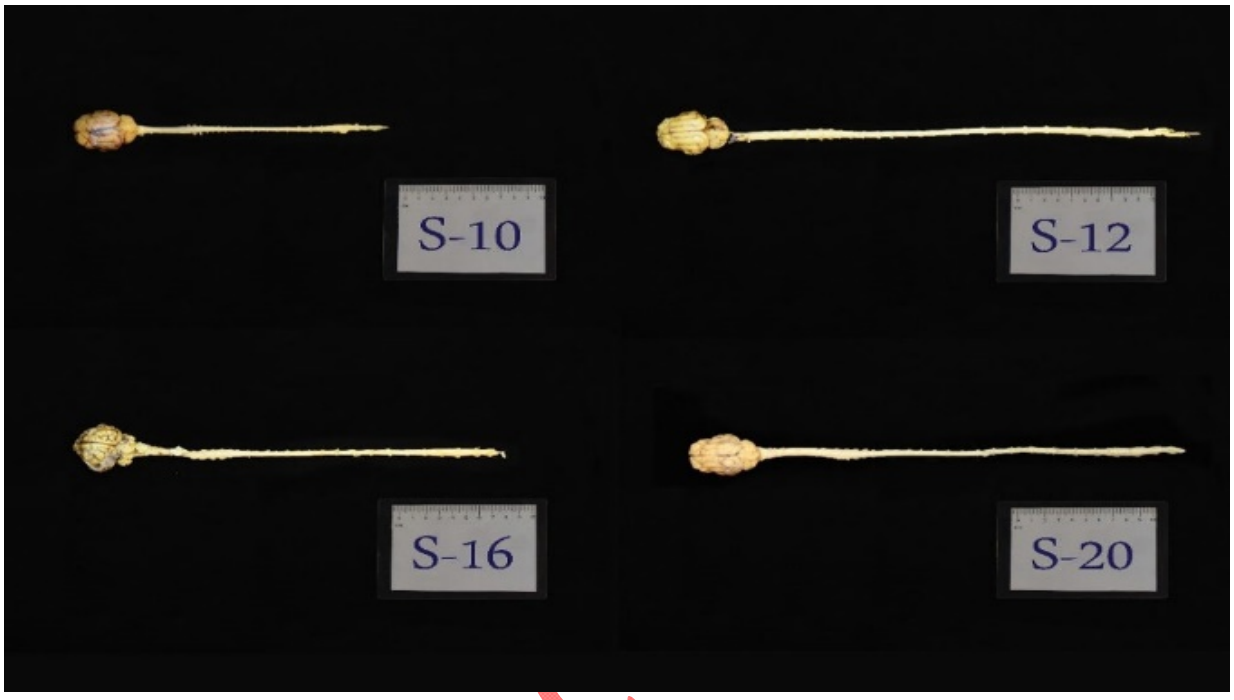

Figure 2.

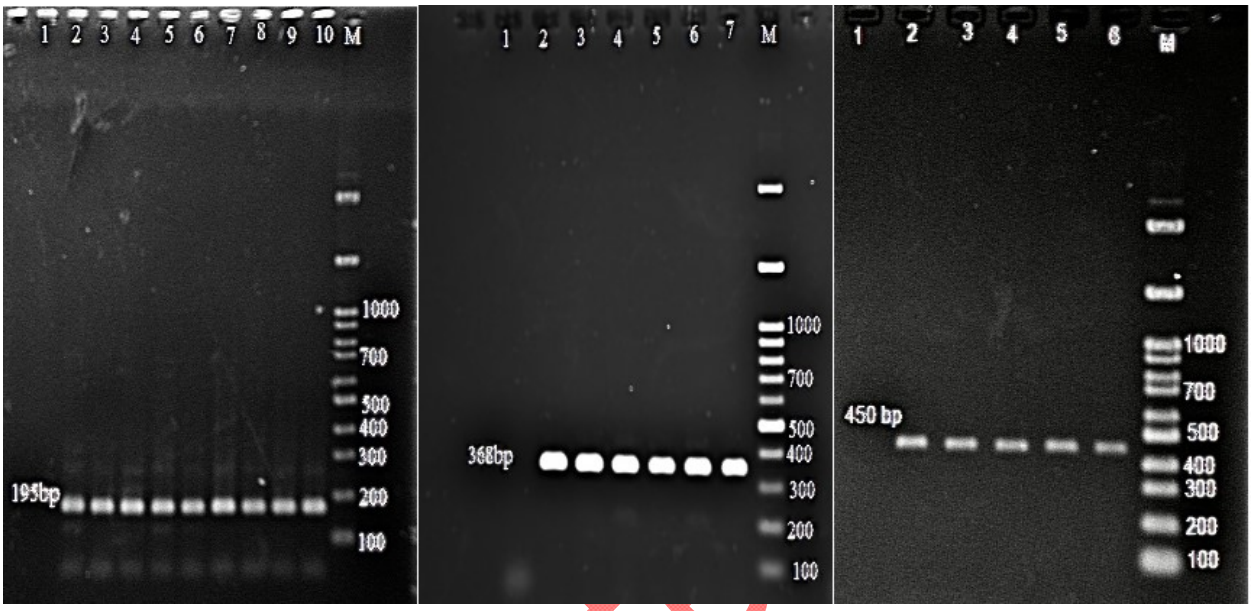

Figure 3.

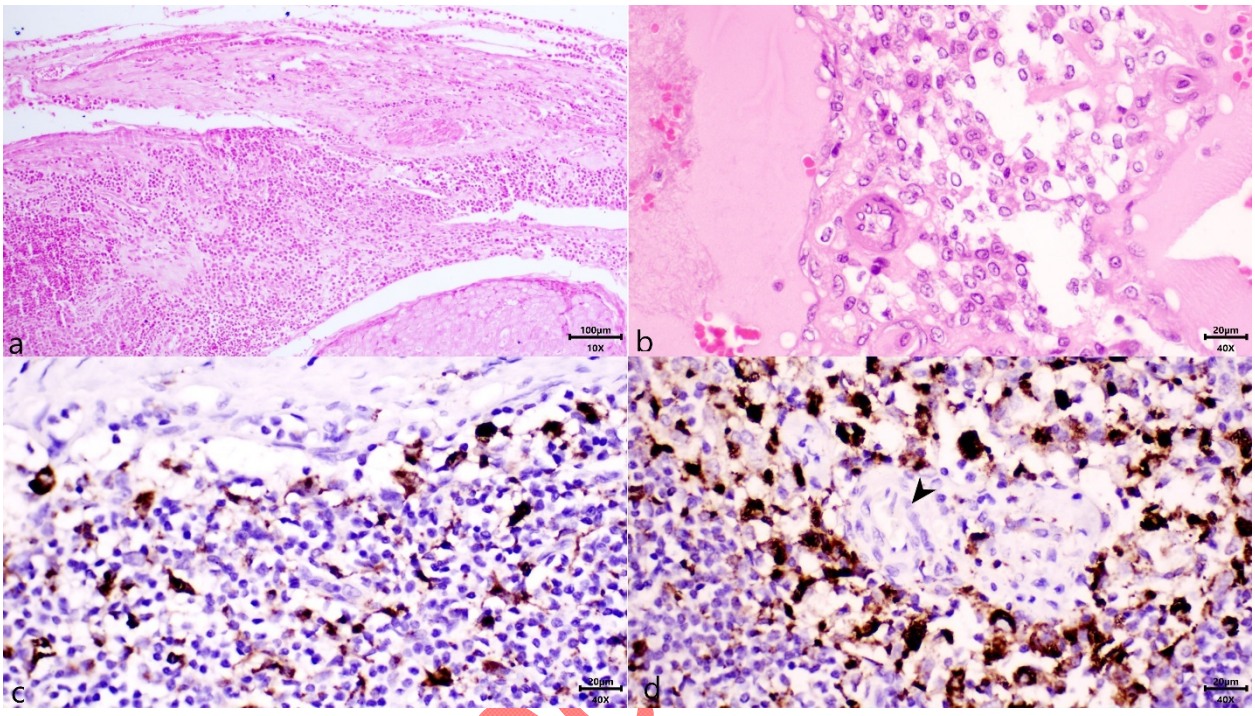

Figure 4.

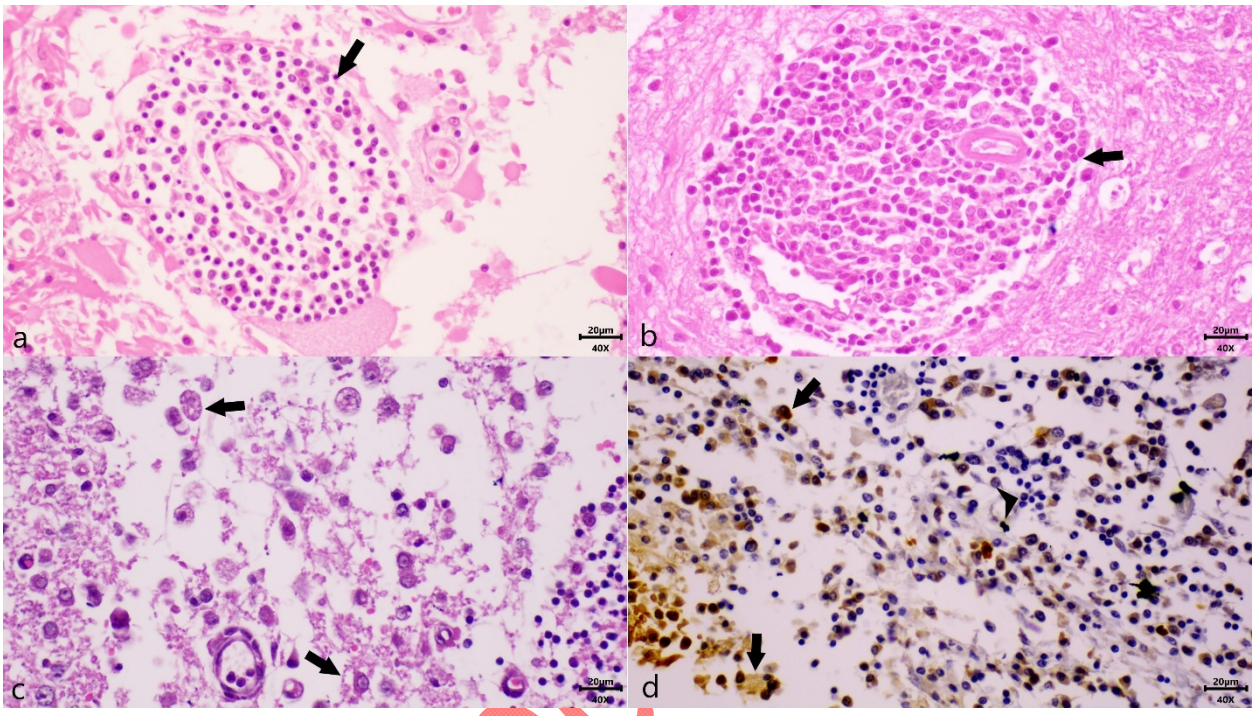

Figure 5.

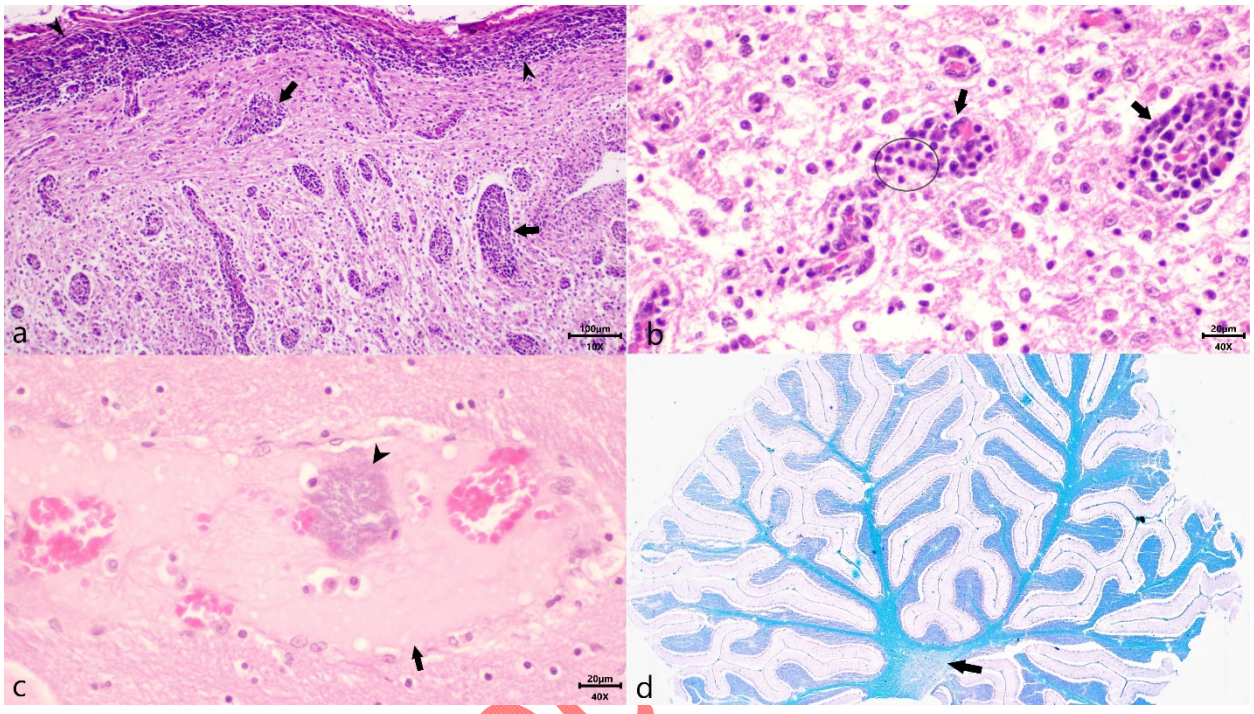

Figure 6.

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