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Neurological diseases of viral origin in cattle in the state of Pernambuco, Brazil: clinical and anatomopathological study

Enfermidades neurológicas de origem viral em bovinos no estado de Pernambuco, Brasil: estudo clínico e anatomopatológico

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Abstract
Studies related to neurological diseases are of great importance in Veterinary Medicine, particularly those involving production animals, such as cattle, due to their wide sanitary and public health significance. Therefore, the current study aims to describe the frequency of occurrence of the main clinical, laboratory, and anatomopathological findings of cattle diagnosed with neurological diseases of viral origin. Screening was performed in the general register of patients diagnosed through anatomopathological and/or complementary examination with illnesses of viral origin, admitted (live or dead) to the Clínica de Bovinos de Garanhuns-UFRPE from January 2009 to December 2019. The information recovered was entered in a database created in the computer program Microsoft Excel 2010®, distributed into clinical, laboratory, and anatomopathological data. The clinical findings on neurological diseases of viral etiology were very varied and non-specific, and the anatomopathological findings, together with laboratory methods, were of fundamental importance for the establishment of the diagnosis. The high frequency of rabies cases in this study demonstrates the importance of this disease for cattle rearing, as well as for Public Health. We emphasize the importance of including malignant catarrhal fever and herpes meningoencephalitis in the differential diagnosis of neurological diseases in the region, as well as the adoption of sanitary measures.
Keywords: clinical findings; rabies; herpes meningoencephalitis; malignant bluetongue; anatomopathological findings.

Resumo
Os estudos relacionados as doenças neurológicas assumem grande importância na Medicina Veterinária, particularmente os que envolvem animais de produção como os bovinos, em virtude da grande importância sanitária e de saúde pública. Nesse contexto, este trabalho teve como objetivo descrever a frequência de ocorrência dos principais achados clínicos, laboratoriais e anatomopatológicos dos bovinos diagnosticados com doenças neurológicas de origem viral. Realizou-se a triagem no livro de registro geral dos pacientes com enfermidades que cursaram com sintomatologia neurológica e que foram diagnosticados através de exame anatomopatológico e/ou complementares com enfermidades de origem viral, os quais deram entrada (vivos ou mortos) na Clínica de Bovinos de Garanhuns-UFRPE no período de janeiro de 2009 a dezembro de 2019. As informações obtidas foram inseridas em um banco de dados elaborado no programa de computador Microsoft Excel 2010® distribuídas em dados clínicos, laboratoriais e anatomopatológicos. Os achados clínicos das enfermidades neurológicas de etiologia viral foram muito variados e inespecíficos, sendo os achados anatomopatológicos, aliados aos métodos laboratoriais, de importância fundamental para o estabelecimento do diagnóstico. A elevada frequência dos casos de raiva neste estudo demonstra a importância sanitária desta enfermidade para a pecuária bovina, como também para a saúde pública. Ressalta-se a importância da inclusão da febre catarral maligna e da meningoencefalite herpética no diagnóstico diferencial das doenças neurológicas na região, assim como a adoção de medidas sanitárias.
Palavras-chave: achados clínicos; raiva; meningoencefalite herpética; febre catarral maligna; achados anatomopatológicos.

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1. Introduction

Studies related to neurological diseases are of great importance in Veterinary Medicine, particularly those involving production animals, such as cattle, due to their great sanitary and public health importance [1,2]. The emergence of bovine spongiform encephalopathy, in the mid-1980s, and its subsequent association with the variant of human Creutzfeldt-Jakob disease (vCJD), highlighted the socioeconomic and health importance of central nervous system diseases in this species, and the need for improvement in differential diagnosis [3]. Neurological diseases are responsible for significant economic losses in Brazilian livestock, showing great relevance in the agricultural scenario due to the frequency with which they occur, often in the form of outbreaks, in many cases presenting low morbidity, but with high lethality rates in affected animals [3,4,5].

In recent years, retrospective studies of the diseases that affect the nervous system of cattle have been carried out in different regions of the country, however, despite the importance of the diagnosis, a significant portion of the cases remain unclear, lacking an etiological diagnosis, representing a constant concern for human and animal health [6,7]. Infections of viral origin assume significant importance, particularly, in greater prominence, those associated with the rabies virus and bovine herpesvirus type 5 (BoHV-5) [4,5,8,9,10,11,12,13,14,15]. Rabies is the most relevant central nervous system disease in cattle in Brazil [16]. In the country, the annual loss of cattle due to rabies is estimated at approximately 17 million dollars or approximately 850,000 head [11]. It is estimated that bovine rabies in Latin America causes annual losses of hundreds of millions of dollars, caused by the death of thousands of head, in addition to the indirect expenses that may occur with the vaccination of millions of cattle and countless post-exposure treatments of people who had contact with animals with a suspected infection [17].

The expansion of information regarding these diseases, as well as other viruses that involve the nervous system of cattle, is of great value for the adoption of measures aimed at the health of the cattle herd. The objective of this study was to describe the frequency of occurrence of the main clinical, laboratory, and anatomopathological findings in cattle diagnosed with neurological diseases of viral origin.

2. Materials and methods

The study was performed at the Clínica de Bovinos de Garanhuns-UFRPE. Initially, screening was carried out in the general record book of patients diagnosed with illnesses that presented with neurological symptoms, diagnosed through anatomopathological and/or complementary exams with illnesses of viral origin, and admitted (alive or dead) to the institution in the period from January 2009 to December 2019. Subsequently, clinical records and *post-mortem* examination records were accessed. The information obtained was entered in a database prepared in the Microsoft Excel 2010® computer program distributed into clinical, laboratory, and anatomopathological data.

As a routine clinical procedure, the animals underwent a clinical examination at the time of hospital discharge, in accordance with the guidelines by Dirksen et al. [18]. Hematological exams (hemogram and determination of total protein and fibrinogen plasmatic concentration) were performed as described by Harvey [19]. The animals that died were submitted to anatomopathological exams [20].

As these are neurological diseases, therapeutic intervention was instituted when there was a possibility of disease regression and clinical indication. According to the evolution and severity of the clinical signs, the animals were clinically monitored, as long as they did not reach situations of terminal suffering, when euthanasia was indicated [21]. Tissue fragments of organs from the thoracic and abdominal cavities, central nervous system, lymph nodes, and skin were collected, fixed in 10% buffered formalin, and histopathological examination was performed [22], using Hematoxylin and Eosin stain (HE).

All animals submitted to necropsy that presented neurological manifestations were tested for rabies. Fragments of the brain (cortex and hippocampus), cerebellum, and spinal cord were sent frozen to the Agricultural Defense and Inspection Agency of the State of Pernambuco (Adagro) for direct immunofluorescence (DIF) and biological testing in mice [23]. Confirmation of the diagnosis of meningoencephalitis due to BoHV-5 or BoHV-1 was based on the suggestive results of the histopathological examination and confirmation of the presence of viral DNA in the nervous system by means of the polymerase chain reaction (PCR) [24]. Both samples preserved in paraffin and frozen were submitted to PCR, as described by Silva [25]. The diagnosis of malignant bluetongue was based on clinical epidemiological and anatomopathological findings. For data analysis, a descriptive statistical model was used, observing the distribution of variables through relative and absolute frequencies for each disease [26].

3. Results and discussion

During the eleven-year period studied, a total of 6,103 cattle were treated, of which 604 (10.1%) were diagnosed with neurological diseases. Of these 604, 21.5% (n=130) had a viral etiology, with 101 (77.7%) cases of rabies, 19 (14.6%) cases of malignant bluetongue, and 10 (7.7%) cases of herpes meningoencephalitis.

3.1 Rabies

Affected cattle had a predominantly paralytic clinical picture, related to spinal cord, brainstem, and cerebellum injuries, together with signs associated with brain injuries (Table 1). These findings have also been reported by other authors. [9,11,13,14,27,28,29,30]. However, it is known that the variation in these clinical findings and the progression of the virus vary depending on the proximity between the site of inoculation and the brain, concentration of the virus in the inoculum, pathogenicity of the viral strain, and immune status of the animal [31].

Table 1. Frequency of occurrence of clinical findings observed in cattle diagnosed with rabies (n=84) from 2009 to 2019 at Clínica de Bovinos de Garanhuns-UFRPE

DISEASE OF VIRAL ORIGIN	CLINICAL FINDINGS	n (n=84)	%
Rabies	Decubitus	63	75.0
	Moderate to severe dehydration	59	70.2
	Anal reflex reduced to absent	47	56.0
	Tail reflex reduced to absent	43	51.2
	Stagger	39	46.4
	Panniculus reflex reduced to absent	38	45.2
	Reduction in the absence of skin reflexes	38	45.2
	Pedaling movements	36	42.9
	Apathetic to depressive behavior	36	42.9
	Ataxia	23	27.4
	Vocalization	20	23.8
	bruxism	19	22.6
	Reduced facial skin sensitivity	16	19.0
	Agitated behavior	14	16.7
	Sialorrhea	13	15.5
	Muscle tremors	12	14.3
	Intention tremors	12	14.3
	Paresis of pelvic limbs	10	11.9
	Pelvic limb paralysis	09	10.7
	Falls	09	10.7
	Strabismus	09	10.7
	Nystagmus	09	10.7
	Seizures	09	10.7
	Walk in circles	09	10.7
	Reduction in tongue tone	09	10.7
	Lumping	09	10.7

Considering the hematological findings, the animals diagnosed with rabies showed alteration only in the leukogram, which presented leukocytosis due to neutrophilia, with a slight regenerative shift to the left, a finding also mentioned by Constable [31]. Elevations in white blood cell counts have also been observed in human rabies patients [32,33]. The increase in the neutrophil count in inflammatory processes of viral origin was reported by Tornquist; Rigas [34]; Webb; Latimer [35]. According to Wood and Queiro-Rocha [36], tissue damage, through the release of pro-inflammatory factors, particularly cytokines, triggers the recruitment of leukocytes from the marginal compartment of the bone marrow into the bloodstream, followed by migration to the injured tissue, with the aim of combating the inflammatory and/or infectious process. It should be noted that the rapid demand for neutrophils depletes the stored segmented reserves and stimulates the production and release of young cells.

Among the macroscopic findings, attention is drawn to the hyperemia of the leptomeninges, present in 27% (27/101) of the animals, also reported by Barros et al. [3], Rissi et al. [29], Braga et al. [37], and Ecco et al. [38]. Another finding that draws attention is the repletion of the urinary bladder, observed in 50% of the animals. Lima et al. [11] previously reported urinary bladder dilatation in only 16% of cattle diagnosed with rabies. This reduced number of macroscopic findings agrees with Constable [31], and Jones, Hunt and King [39], who state that the lesions are limited to the central nervous system and only detected in the histopathological examination.

The histopathological findings were characterized by a mononuclear inflammatory infiltrate, consisting predominantly of lymphocytes, plasmocytes, and rare macrophages, arranged in the perivascular spaces of the brain and leptomeninges (non-suppurative meningoencephalitis), fig. 02. Eosinophilic viral inclusion corpuscles were observed in the cytoplasm of neurons, sometimes multiple inclusions ranging from 1-10µm in diameter. Additional less frequent findings included focal or diffuse microgliosis, neuronal chromatolysis, neuronal necrosis, and neuroniophagia. In some cases, myelitis and lymphoplasmacytic ganglioneuritis were also observed. In this study, 97% of the cases were positive in direct immunofluorescence (DIF) and in the histopathological examination, when performed. As previously observed in other works on rabies in herbivores [11], inflammatory alterations and the characteristic Negri bodies can be present throughout the nervous system, but in cattle they tend to be more frequent in the cerebellum [11]. The frequency of appearance of Negri bodies is inversely proportional to the degree of inflammation and they are not present in up to 30% of cases of rabies, as certain strains of the virus do not produce inclusion bodies [11, 31]. Furthermore, according to Langohr et al. [28] the non-visualization of Negri bodies in some cases of rabies may be directly associated with the survival time of the animal after the infection, that is, the longer the clinical course, the greater the probability of detecting the bodies.

3.2 Malignant Catarrhal Fever (MCF))

MCF was the second most frequent disease among viral etiologies. Reports by Silva et al. [40], Souza et al. [43], and Macêdo et al. [42], demonstrate that MCF is endemic in the Northeast. The most common manifestations in the current study are distributed in Table 2, as also mentioned in previous works [10,42,43,44,45,46,47]. Clinical signs were more evident in animals that survived longer [48].

Table 2. Frequency of occurrence of clinical findings observed in cattle diagnosed with MCF (n=17) from 2009 to 2019 at Clínica de Bovinos de Garanhuns-UFRPE.

DISEASE OF VIRAL ORIGIN	CLINICAL FINDINGS	n (n=17)	%
MCF	Corneal opacity	16	94.1
	Enlarged lymph nodes	14	82.4
	Sialorrhea	12	70.6
	Fever	12	70.6
	Moderate to severe dehydration	12	70.6
	Apathetic to depressive behavior	11	64.7
	Absence of visual acuity	09	52.9
	Catarrhal nasal discharge	09	52.9
	Erosions and detachment of oral epithelium	07	41.2
	Changes to lung auscultation	07	41.2
	Erosions and detachment of nasal epithelium	06	35.3
	Blepharospasms	06	35.3
	Pedaling movement	05	29.4
	Hypopyon	05	29.4
	Serous/mucous/catarrhal nasal discharge	04	23.5
	Muscle tremors	04	23.5
	Opisthotonos	04	23.5
	Intention tremors	04	23.5
	Ataxia	04	23.5
	Bruxism	04	23.5
	Reduced visual acuity/reduced threat reflex	03	17.6
	Hypermetria	02	11.8
	Hyperexcitability	02	11.8
	Pushes head against obstacles	02	11.8
	Reduced anal sphincter reflex	02	11.8
	Absent eyelid reflex	02	11.8
	Stagger	02	11.8
	Uncoordinated walking	01	5.9
	Walk aimlessly	01	5.9
	Vocalization	01	5.9
	Seizures	01	5.9

In animals affected by MCF, at the time of hospital discharge, no alterations were observed in the mean values of the erythrogram, as well as in the total leucometry, with the values being within the normal range for the species [49]. However, the mean values observed in the leukogram of the neutrophil:lymphocyte ratio are 1:1 and not 1:2, as is generally observed in adult cattle. These findings differ from leukopenia due to agranulocytosis cited in this disease by Constable, [31] and leukocytosis due to neutrophilia reported by Mendonçaa et al. [44]. Additionally, in cases of MCF, the increase in the mean value of plasmatic fibrinogen concentration without observation of leukocytosis corroborates with Taylor [49], who reported measuring this protein as the best indicator of inflammatory disease in cattle. According to Eckersall [50] and O´Mahony et al. [51], circulating concentrations of acute phase proteins are related to the severity of organ dysfunction and, therefore, their quantification readily provides a means of assessing the presence and extent of the inflammatory process. Thus, the fibrinogen response probably stems from the intense inflammatory reaction resulting from generalized vasculitis, which represents a severe inflammatory process in cases of MCF.

Necropsy findings included fibrin-necrotic material in the mucous membranes of the respiratory tract (06/19), hyperemia of the telencephalic vessels (05/19), tracheitis (03/19) fig. 01, hyperemia of the leptomeningeal vessels (04/19), edema of the folds of the abomasum and mesentery (01/19), hepatomegaly (04/19), pulmonary edema (04/19), rumenitis/abomasitis/reticulitis (02 /19), petechiae and cardiac suffusions (3/19), and hypopyon (5/19), as also found in other studies [43,45,46,52, 53]. In the cases reported in Goiás by Terra et al. [14], there were no significant macroscopic findings.

Histopathological findings in the nervous system were characterized by a mononuclear inflammatory infiltrate, composed of lymphocytes, plasmocytes, and macrophages, and hyaline degeneration of the walls of arterioles (necrotizing vasculitis), particularly those of small caliber present in the *carotid rete mirabile*, fig. 02. The inflammatory infiltrate sometimes extended to perivascular spaces and leptomeninges. Vascular lesions were also observed in arterioles present in other tissues, such as the kidneys, liver, lymph nodes, and mucous membrane of the alimentary, respiratory, urinary, and genital tracts, almost always associated with ulceration of the overlying epithelium. The visualization of multisystem vasculitis, accumulations of mononuclear inflammatory cells in various tissues, and necrosis of the lining epithelia strongly contribute to the establishment of the histopathological diagnosis of MCF [54] as described in the states of Mato Grosso do Sul and São Paulo by Lemos et al. [10], in Paraíba by Macêdo et al. [42], in Rio de Janeiro by Galvão et al. [46], in Espírito Santo by Carmo et al. [55], and in Bahia by Peixoto et al. [52].

3.3 Herpesvirus meningoencephalitis

In the current work, among diseases of viral etiology, meningoencephalitis due to herpesvirus had a frequency of 7.7% (10/604), being lower than rabies and

Figure 1. Viral neurological diseases in cattle diagnosed at Clínica de Bovinos de Garanhuns-UFRPE. A) Rabies: Animal in recumbency with pedaling movements B) Rabies: Urinary bladder distension. C) Malignant catarrhal fever: Erosions/ulcerations in the region of the glottis and epiglottis. D) Malignant catarrhal fever: Erosions on the tongue. E) Herpetic meningoencephalitis: Absent anal sphincter reflex. F) Herpetic meningoencephalitis: Reduced sensitivity of the face.

MCF, as reported in other regions in the northeastern semi-arid region [13]. This result differs from several retrospective studies of diseases that affect the central nervous system, carried out in different regions of Brazil in recent years, in which the highest occurrences are predominantly attributed to rabies followed by meningoencephalitis due to herpesvirus. Possibly, the low occurrence may be related to the difficulty of diagnosis, since it requires laboratory resources, such as the Polymerase Chain Reaction or immunohistochemistry.

The clinical signs observed are shown in Table 3. The findings are similar to those described by other authors in cases of the disease [5,13,56,57,58,59]. These symptoms, as well as their intensity, varied between animals and throughout evolution. In experimental infection, some animals did not exhibit clinical manifestations, however the histopathological examination confirmed that all calves studied exhibited an encephalic inflammatory process, indicating that the encephalitis caused by BoHV-5 may be mild and asymptomatic [60].

Table 3. Frequency of occurrence of clinical findings observed in cattle diagnosed with herpetic meningoencephalitis (n=09) from 2009 to 2019 at Clínica de Bovinos de Garanhuns-UFRPE

DISEASE OF VIRAL ORIGIN	CLINICAL FINDINGS	n (n=09)	%
Meningoencephalitis	Moderate to severe dehydration	08	88.9
	Reduced anal sphincter reflex	07	77.8
	Threat reflex reduced to absent	05	55.6
	Facial sensitivity reduced to absent	05	55.6
	Reduced thoracic and pelvic limb contraction reflex	05	55.6
	Reduced tail reflex	05	55.6
	Absent olfactory reflex	04	44.4
	Reduced panniculus reflex	04	44.4
	Reduced forelimb and forelimb skin sensitivity	04	44.4
	Sensitivity of the nasal mucosa reduced to absent	03	33.3
	Ataxia	03	33.3
	Reduced to absent pupillary reflex	03	33.3
	Positive proprioceptive maze test	03	33.3
	Apathetic to depressive behavior	03	33.3
	Reduced thoracic and pelvic limb twitch reflexes	03	33.3
	Reduced lingual tone	02	22.2
	Strabismus	02	22.2
	Intention tremors	02	22.2
	Paresis of thoracic and pelvic limbs	02	22.2
	Pedaling movements	02	22.2
	Strabismus	02	22.2
	Intention tremors	02	22.2
	Muscle tremors	02	22.2
	Stagger	02	22.2
	Uncoordinated walking	02	22.2
	Catarrhal nasal discharge	01	11.1
	Aggressiveness	01	11.1
	Bruxism	01	11.1
	Vocalization	01	11.1
	Depression	01	11.1
	Oblivious to the environment	01	11.1
	No obstacle avoidance	01	11.1
	Walk in circles	01	11.1
	Walk aimlessly	01	11.1
	Falls	01	11.1
	Hyperexcitability	01	11.1
	Pushes head against obstacles	01	11.1
	Nystagmus	01	11.1

The animals diagnosed with herpetic meningoencephalitis showed neutrophilic leukocytosis, with a slight regenerative left shift and plasma fibrinogen and erythrogram values within the normal range. Results consistent with a tendency to leukocytosis accompanied by increased segmented neutrophils and normal plasma fibrinogen levels were reported by Lisbôa et al. [61]. In these cases, the increase in the number of circulating neutrophils is due to the stimulus caused by the stressors that trigger meningoencephalitis [62].

In most of the cases observed in this study, necropsy findings were not prominent, as described by Rissi et al. (57) and Oliveira et al. (59). When present, such findings consisted of multifocal yellowish and soft areas in the telencephalic cortices, characteristic of cerebral gray matter malacia, and hyperemia of the leptomeningeal vessels (63).

The histopathological findings were characterized by a mononuclear inflammatory infiltrate consisting of lymphocytes, plasma cells, and macrophages in the perivascular spaces and extending to the neuropil and adjacent leptomeninges. In the gray matter, retracted, hypereosinophilic neuronal cell bodies with a pyknotic nucleus (cortical laminar necrosis) were observed, sometimes associated with neuroniophagia, gliosis, vasculitis, edema, and multifocal areas of vacuolization and malacia, permeated by *Gitter* cells. Occasional astrocytes and neurons with eosinophilic viral intranuclear inclusion bodies were also seen (Fig. 2). Cases of herpetic meningoencephalitis present areas of malacia as the main histopathological finding [56,63,64], most often located in the

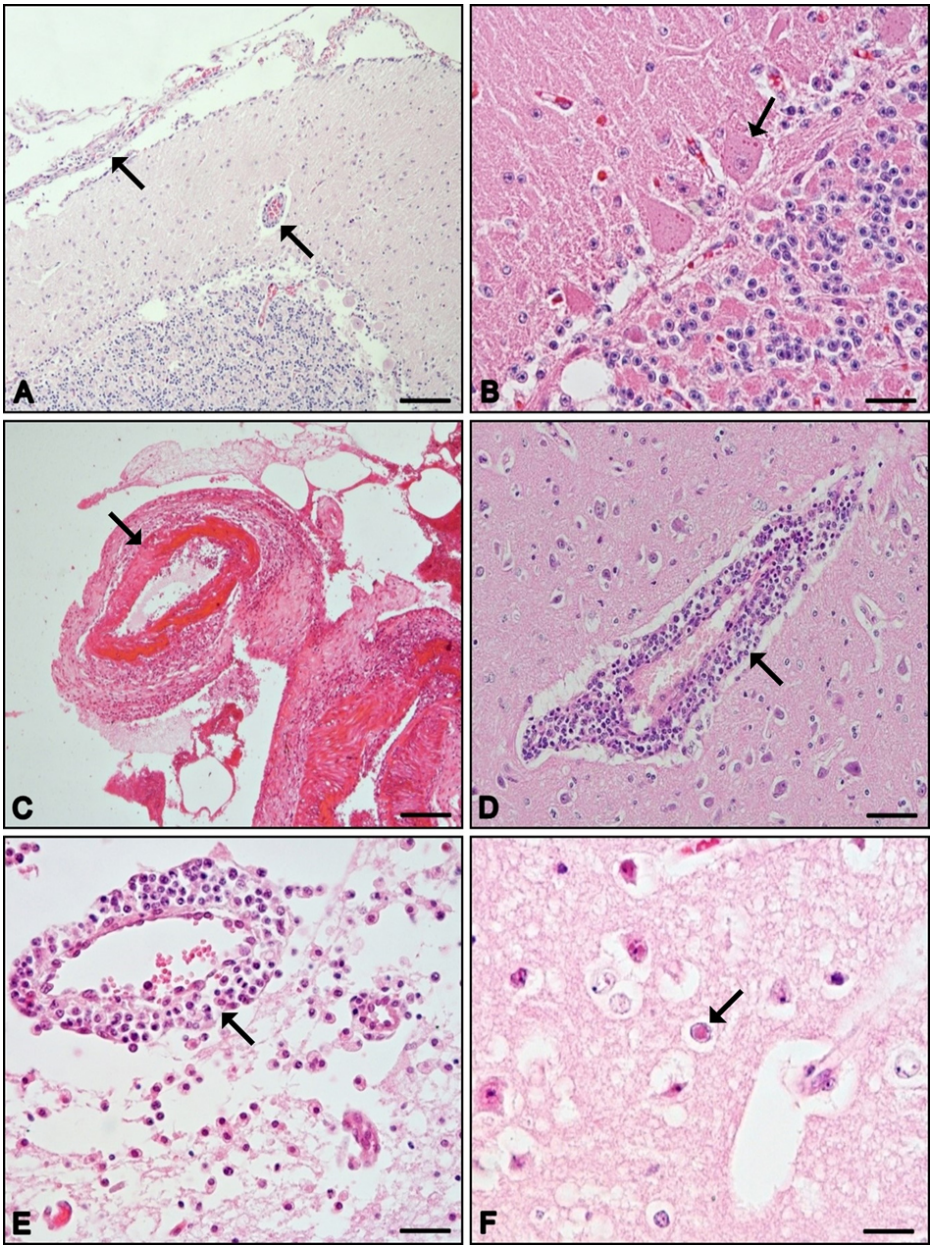

Figure 2. Viral neurological diseases in cattle diagnosed at Clínica de Bovinos de Garanhuns-UFRPE. A) Rabies: Cerebellum. Mononuclear inflammatory infiltrate in the perivascular space and leptomeninges. HE. Obj. 25x. B) Rabies: Cerebellum. Eosinophilic viral inclusion bodies in the cytoplasm of Purkinje neurons. HE. Obj. 40x. C) Malignant catarrhal fever. *carotid rete mirabile*. Mononuclear inflammatory infiltrate associated with hyaline degeneration in the wall of arterioles (necrotizing vasculitis). HE. Obj. 25x. D) Malignant catarrhal fever. Brain, temporal cortex. Marked mononuclear inflammatory infiltrate in the perivascular space. HE. Obj. 40x. E) Herpetic meningoencephalitis. Frontal cortex, gray matter. Perivascular mononuclear inflammatory infiltrate and Gitter cells in the adjacent neutrophil (malacia). HE. Obj. 40x. F) Herpetic meningoencephalitis. Frontal cortex, gray matter. Eosinophilic intranuclear viral inclusion corpuscle in astrocyte. HE. Obj. 40x.

frontal cortex, although other regions can be affected [64]. This is probably related to the usual route of access of the virus to the nervous system through the olfactory nerves [63].

Animals that simultaneously developed polioencephalomalacia and herpesvirus meningoencephalitis had more pronounced malacia lesions, corroborating the findings of David *et al*. [65]. Although the characteristic lesion of non-suppurative meningoencephalitis is attributed to BoHV5, the same lesion may also be present in some cases of BoHV1 infection due to its tropism for the central nervous system, as well as cases of rabies and malignant bluetongue [03].

Therefore, it is necessary to confirm the infection by means of diagnostic techniques that allow the distinction not only between different neurological disorders, but also between types 1 and 5 of bovine alpha-herpesvirus. The distribution of diseases of neurological origin may vary due to the regional particularities of each place where it occurs. For this reason, it is necessary to identify regional circulation agents so that the appropriate strategic actions can be conducted to minimize losses [15].

4. Conclusions

The clinical findings of neurological diseases of viral etiology are very varied and nonspecific, and the anatomopathological findings, combined with laboratory methods, are of fundamental importance for establishing the diagnosis. The high frequency of rabies cases in this study demonstrates the importance of this disease for cattle farming, as well as for public health, as it is a lethal zoonosis for both species, and the adoption of preventive health measures in the region is vital. It is important to include malignant bluetongue and herpetic meningoencephalitis in the differential diagnosis of neurological diseases in the region, as well as disseminating the adoption of sanitary measures.

Conflict of interests

The authors declare no conflict of interest.

Author contributions

Conceptualization: M. I. Souza, J. A. B. Afonso and C. L. Mendonça. Data curation: M. I. Souza, J. A. B. Afonso, C. L. Mendonça, R. J. C. Souto, A. I. Conceição and N. A. Costa. Methodology: M. I. Souza, J. A. B. Afonso, C. L. Mendonça, E. P. F. Souto and B. P. Silva. Visualization: M. I. Souza, J. A. B. Afonso, C. L. Mendonça and A. I. Conceição. Project administration: J. A. B. Afonso. Writing (original draft): M. I. Souza, J. A. B. Afonso and C. L. Mendonça. Writing (review & editing): M. I. Souza, J. A. B. Afonso, C. L. Mendonça and A. I. Conceição.

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