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Neurological diseases of cattle diagnosed by histopathology in Minas Gerais

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Abstract

This study was based on analysis of the central nervous system from cattle that died after developing neurological disease in the State of Minas Gerais from 2004 to 2010. Samples were analyzed by histopathology, histochemistry, and anti-*Listeria monocytogenes* immunohistochemistry. The frequency of positivity for the techniques used and distribution were determined, and the results were analyzed by Fisher's exact test. Microscopic changes were observed in 29.5% (290/982) of bovine central nervous system samples examined. Inflammatory changes were the most frequent lesions (87.2% - 253/290) with 80% of cases (232/290) presenting non suppurative inflammation. Through histopathologic analyses, presumptive or conclusive etiology was obtained in 25.2% (73/290) of the samples. Etiologic diagnosis included inflammation by viruses (bovine herpesvirus infection in six samples; ovine herpesvirus-2 infection in eight samples); and bacteria (bacterial infection in 34 samples; and tuberculosis in six samples). Circulatory changes were evident in 26 cattle being nine cases of cerebral babesiosis. Degenerative lesions were detected in eight samples. One congenital change (cerebellar abiotrophy) and one neoplasm (astrocytoma) were identified. Neurological diseases other than rabies were diagnosed in Minas Gerais, and the use of histopathology allowed a more accurate differential diagnosis and a higher rate of conclusive diagnoses.

Key words: cattle, neurological diseases, health surveillance, differential diagnosis.

Introduction

Neurological diseases are very important causes of mortality and economic losses for the cattle industry in Brazil (6, 15, 16, 18, 21, 24, 28, 32, 35, 41, 42). More recently, an accurate and conclusive diagnosis in cases of neurological diseases became even more important in order to meet international animal health standards (5), particularly after the bovine spongiform encephalopathy was identified as a threat for animal and human health (45).

The State of Minas Gerais has the second largest bovine herd in Brazil (22), but information regarding bovine neurological diseases in this State is largely restricted to the diagnosis and epidemiologic assessment of rabies (29, 32, 44), with the exception of a few isolated reports of other diseases (2, 15, 18, 30, 33). The Animal Health Laboratory of the Instituto Mineiro de Agropecuária (LSA/IMA) is in charge of diagnostic tests for rabies and transmissible spongiform encephalopathies (TSEs) in animals in Minas Gerais, receiving approximately 200 central nervous system (CNS) samples from cattle with neurologic diseases annually. Approximately 40% of these samples test positive for rabies by direct fluorescent antibody test and biological test (32) and so far 100% of them have been negative for TSEs (unpublished data). Thus, conclusive diagnoses of the remaining cases may provide the basis for appropriate control of neurological diseases in cattle. Therefore, the goal of this study was to employ histopathology techniques for the diagnosis of neurologic diseases in cattle in the State of Minas Gerais.

Material and methods

The samples analyzed in this study were obtained from 982 cattle that died or were euthanized due to neurological signs and were negative for rabies. Samples were collected by official or private veterinary practitioners from all regions of the State of Minas Gerais from 2004 to 2010. A standard questionnaire (5) was applied regarding every sample. Samples were submitted to the laboratory fixed in 10% formalin. Formalin-fixed samples were processed for paraffin embedding and stained with hematoxylin and eosin. Sections with granulomatous lesions were stained with Ziehl-Nielsen.

Morphological changes were described in CNS and classified as circulatory, inflammatory, degenerative, or neoplastic. Presumptive or conclusive etiologic diagnoses were based on observation of typical lesions or intralesional detection of acid-fast bacteria through special staining.

Histological sections from CNS of 34 cattle with lesions compatible with bacterial infection (suppurative inflammation) were processed for immunohistochemistry. Sections were treated with 0.05% proteinase K for 10 minutes for antigen retrieval, washed in PBS for 5 minutes. Endogenous peroxidase was inhibited by incubating with 10% hydrogen peroxide for 30 minutes. Sections were then incubated with 2.5% skim milk in PBS at 37ºC for 45 minutes. An anti-*L. monocytogenes* serum (Listeria O antiserum poly. Serotypes 1 and 4, Difco, USA) was used as primary antibody with a 1:100 dilution for 45 minutes at 37ºC. Sections were washed three times in PBS for 5 minutes each, and then incubated with the secondary biotinylated antibody (LSAB, Dako, USA) at 37ºC for 20 minutes, washed three times in PBS for 5 minutes, and incubated with the LSAB reagent (LSAB, Dako, USA) for 20 minutes. Sections were washed three times in PBS for 5 minutes, and then developed with AEC (Aminoethylcarbazole Substrate Chromogen System, Dako, USA) for 10 minutes and washed with distilled water. Sections were counterstained with Mayer's hematoxylin for 30 seconds, washed and mounted with Faramount (Dako, USA).

Frequencies of morphologic diagnoses as well as frequency of lesions or etiologic diagnoses according to the CNS sample (i.e. cerebrum, cerebellum, trigeminal ganglion, rostral epidural *rete mirabile*, pituitary gland, thalamus, brain stem, and cervical spinal cord) were calculated. Data were analyzed by descriptive statistics, and frequencies were compared by using the Fisher's exact test. Statistical analyses were performed using the Instat software (Graphpad Instat, USA).

Results and discussion

From 2004 to 2010, CNS samples from 982 cattle with neurological signs and that tested negative for rabies were evaluated by histopathology. Frequencies of CNS regions sampled from 982 cattle and evaluated microscopically were: cerebrum 77.09% (757), cerebellum 73.32% (720), pituitary 12.02% (118), rostral epidural *rete mirabile* 12.93% (127), trigeminal ganglion 14.46% (142), thalamus 19.96% (196), midbrain 55.80% (548), pons 63.03% (619), medulla oblongata 63.65% (625), and cervical spinal cord 3.26% (32). The presence of cerebrum and/or cerebellum in most samples indicates collection also directed to fragments of these regions without prioritizing systematic collection of various brain regions, which is essential for a thorough and definitive diagnosis of various CNS diseases of cattle.

Two hundred and ninety bovine CNS (29.5%) had histopathologic changes (Fig. 1A). Inflammatory changes, classified as encephalitis, meningitis, or meningoencephalitis were the most frequent lesions corresponding to 87.2% (253/290 - Fig. 1B). Nonsuppurative inflammation was the most common finding (91.7% - 232/253). Circulatory changes were evident in 26 cattle. Degenerative lesions classified as polioencephalomalacia were detected in eight samples and 15-month-old Nelore ox had cerebellar abiotrophy (33). Neoplastic changes were identified in only one case.

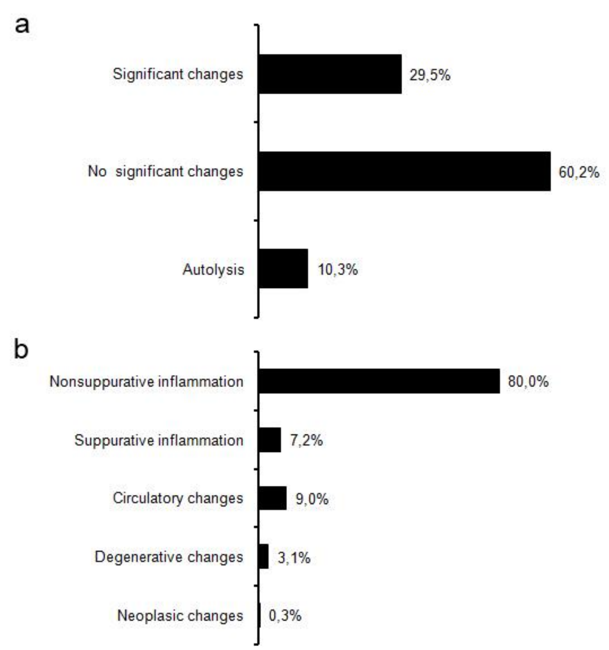

Figure 1. Histopathologic analysis of CNS samples from cattle with neurological syndrome and negative for rabies submitted to the LSA/IMA 2004 to 2010. (a) Frequency of pathological changes in CNS samples from 982 cattle with neurological syndrome. (b) Frequency of morphological diagnoses in samples of CNS from 290 cattle with microscopic changes.

Non suppurative inflammation was observed in several CNS fragments without a predilection for any part of the CNS (p>0.05) (Table 1). However, suppurative inflammation was observed more frequently in the midbrain, pons, and medulla oblongata (p=0.01). As expected, the majority (82.9%) of degenerative disorders characterized by polioencephalomalacia was observed in the cerebrum (p=0.0001).

Histopathologic analyses allowed an etiologic diagnosis in 25.2% (73/290) of the samples, either based solely on morphological changes considered characteristic of a given disease (presumptive diagnosis), or associated with histochemistry and immunohistochemistry (conclusive diagnosis). Table 2 summarizes the presumptive or conclusive diagnoses obtained in this study.

Eight cattle had degenerative changes in the brain, which were characterized by malacia or neuronal necrosis in the gray matter, accumulation of gitter cells, and hypertrophy of the vascular endothelium. Considering that only degenerative changes, with no evidence of inflammation were observed in these cattle, we confirmed the morphologic diagnosis of polioencephalomalacia (PEM). There are several causes associated to PEM such as sulphur, lead or salt poisoning, sudden changes in feedstuff, levamisole or thiabendazole administration, ingestion of thiaminase-rich plants, and bovine herpesvirus -5 (BoHV-5) infection, which is usually associated to meningoencephalitis (13, 27, 36, 43). The diagnosis of PEM is based on characteristic histopathologic changes. However, identification of the cause is often challenging since it may be triggered by several factors, and association of epidemiological data and gross findings are required to establish the etiology of the process (27, 31, 43). PEM have been reported in Minas Gerais, and these cases were likely associated to nutritional factors (15, 30).

Six samples had conclusive diagnosis of BoHV 1/5-induced lesions only by microscopic evaluation. All these samples had mild multifocal inflammatory changes in the cerebrum (most evident in the frontal cortex) extending to the cerebellum, thalamus and brainstem, and in two samples had also cortical necrosis (polioencephalo-

Table 1. Frequency of histopathologic changes according to CNS fragments from 290 cattle analyzed by Animal Health Laboratory of the Instituto Mineiro de Agropecuária from 2004 to 2010.

	Central Nervous System fragments % (absolute value)											
	Cerebrum	Cerebellum	Pituitary	*Rete mirabile*	Trigeminal ganglion	Thalamus	Midbrain	Pons	Medulla	Spinal cord	Total	P value
HH	28.3 (274)	15.5 (150)	0.7 (7)	0.4 (4)	0.0 (0)	4.8 (46)	16.8 (162)	17.1 (165)	16.0 (155)	0.4 (4)	967	>0.05
NS	23.8 (167)	17.8 (125)	0.4 (3)	0.7 (5)	2.8 (20)	3.8 (27)	14.7 (103)	17.0 (119)	18.7 (131)	0.3 (2)	702	>0.05
SI	12.0 (12)	13.0 (13)	2.0 (2)	2.0 (2)	2.0 (2)	6.0 (6)	21.0 (21)	21.0 (21)	21.0 (21)	0.0 (0)	100	0.01
MS	82.9 (63)	3.9 (3)	0.0 (0)	0.0 (0)	0.0 (0)	2.6 (2)	2.6 (2)	3.9 (3)	3.9 (3)	0.0 (0)	76	0.0001
CA	0.0 (0)	100.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1	ND
NE	100.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1	ND
Total	20.8 (872)	18.2 (763)	2.8 (118)	3.1 (129)	3.4 (143)	4.9 (205)	14.0 (586)	15.9 (663)	16.0 (670)	0.8 (33)	4182	

HH - Hyperemia and/or hemorrhage, NS - Nonsuppurative inflammation, SI- Suppurative inflammation, MS - Malacia and/or spongiosis, CA – Cerebellar abiotrophy, NE – Neoplasia, ND – Not determined.

malacia). Eosinophilic intranuclear inclusion bodies were observed in neurons and astrocytes in the gray matter of cerebrum, and they were particularly more evident in tissues adjacent to areas of malacia. All these findings allowed a conclusive diagnosis (11, 14, 36, 37, 39) (Fig. 2).

CNS samples from three cattle had histopathologic changes characterized by fibrinoid vasculitis in the *rete mirabile* (Fig. 3), which were compatible with ovine herpesvirus-2 (OvHV-2) infection, i.e. cases of malignant catarrhal fever (17, 34). This change was associated with a nonsuppurative or necrotizing meningoencephalitis. In addition, five other cattle had fibrinoid vasculitis in randomized CNS vessels associated with meningoencephalitis. Given the absence of changes suggestive of infection by any other pathogen, these later five cases were interpreted as presumptive diagnosis of OvHV-2 infection. These results, along with other reports in the literature (21, 34), indicate the OvHV-2 presence in cattle in Minas Gerais (12). OvHV-2 infection has been described in several regions of Brazil (6, 10, 21, 23, 25, 26, 34). Therefore, these findings reinforce the importance of obtaining adequate and representative CNS samples in cases of neurological disease.

Thirty-four cattle had lesions suggestive of acute bacterial infection, characterized by suppurative inflammation, thromboembolism and/or microabscesses. Four samples had histological changes compatible with thrombotic meningoencephalitis caused by *Histophilus somni*. Histopathologic changes including lymphohistiocytic encephalitis with fibrinoid vasculitis, thrombosis, necrosis and/or multifocal abscesses were seen in several CNS fragments, but these lesions were more evident in the cerebrum, brainstem, and thalamus (Fig. 4A and 4B). *H. somni* should be considered in the differential diagnosis in these cases, but other causes of thromboembolism including valvular endocarditis or omphalophlebitis must also be considered as primary causes (4). There are reports of infection by *H. somni* in the CNS of cattle in Brazil, which were based only on histopathologic changes, i.e. a presumptive diagnosis (16) or with molecular confirmation (20).

Table 2. Presumptive or conclusive diagnoses obtained by histopathology in 290 cattle with histopathologic changes in the CNS, analyzed by Animal Health Laboratory of the Instituto Mineiro de Agropecuária from 2004 to 2010.

Diagnoses	# samples	Morphological changes	n
BoHV infection	6 (8.2%)	Non-suppurative necrotizing encephalitis	3
		Non-suppurative encephalitis and eosinophilic intranuclear inclusion body in neurons and astrocytes	3
OvHV-2 infection	8 (11.0%)	Fibrinoid vasculitis in *rete mirabile*	3
		Random fibrinoid vasculitis	5
Acute bacterial infection	34 (46.6%)	Suppurative encephalitis, meningitis or meningoencephalitis	14
		Suppurative meningoencephalitis with abscesses and /or vasculitis	3
		Nonsuppurative meningoencephalitis with abscesses	10
		Thrombotic meningoencephalitis	3
		Abscesses or microabscesses and malacia	4
Tuberculosis	6 (8.2%)	Granulomatous meningoencephalitis with resistant acid-fast bacilli	6
Polioencephalomalacia	8 (11.0%)	Malacia of gray matter with neuronal necrosis and gitter cells and absence of inflammation	8
Cerebral babesiosis	9 (12.3%)	Intense and diffuse cerebral hyperemia associated with parasitic intraerythrocytic forms compatible with *Babesia bovis*	9
Cerebellar abiotrophy	1 (1.4%)	Atrophy of the cells of Purkinje and granular and molecular layers of cerebellum.	1
Astrocytoma	1 (1.4%)	Neoplastic proliferation with compatible features	1
Total	73 (100%)		73

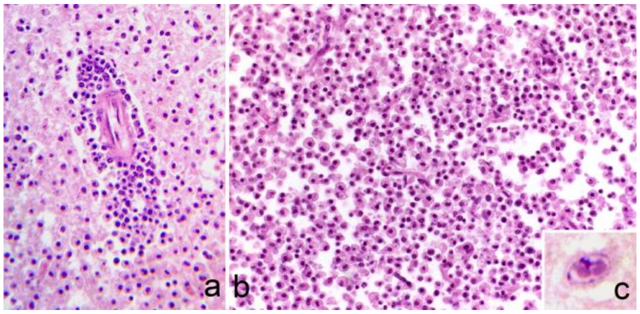

Figure 2. Bovine, brain, histological changes consistent with BoHV-5. (a) moderate lymphohistiocytic perivascular infiltrate, (b) malacia gray matter, characterized by numerous gitter cells associated with hypertrophy of the vascular endothelium. HE, 40X. (**c**) Eosinophilic intranuclear inclusion body in neuron. HE, 100X.

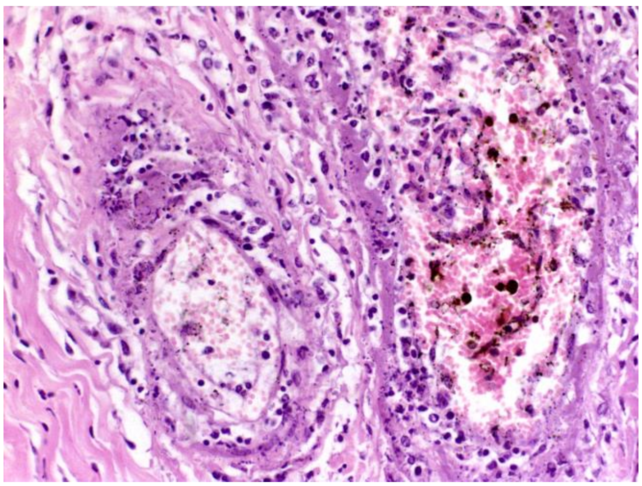

Figure 3. Bovine, rostral epidural *rete mirabile*, histopathologic changes consistent with infection with OvHV-2. Diffuse fibrinoid vasculitis in *rete mirabile*. HE, 40X.

Five cattle had histopathologic changes characterized by nonsuppurative meningoencephalitis associated with multifocal micro-abscesses that led to a presumptive diagnosis of *L. monocytogenes* infection (Fig. 5A). Meningoencephalitis in these cases had a multifocal distribution affecting several CNS fragments, with micro-abscesses concentrated in the brainstem. Immunohistochemistry confirmed only one of these cases (Fig. 5B). Other important causes of micro-abscesses or abscesses in the CNS are umbilical sepsis, extension otitis, and sinusitis (4). Three other samples with lesions suggestive of bacterial infection, but without micro-abscesses in the brainstem were positive for *L. monocytogenes* by immunohistochemistry. Although rhombencephalitis is a classical presentation of CNS listeriosis in ruminants, meningitis or meningoencephalitis have also been reported (9, 38).

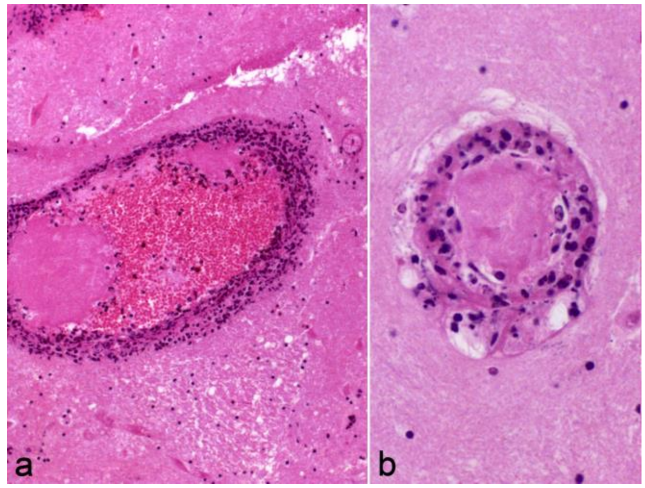

Figure 4. Bovine, thalamus, microscopic alterations compatible with thrombotic meningoencephalitis. (a) Diffuse and moderate lymphohistiocytic perivascular infiltrate, associated with fibrinoid vasculitis and neutrophils, vascular thrombosis and necrosis of the adjacent neuropil. HE, 20X (b) Fibrinoid and neutrophilic vasculitis associated with vascular thrombosis. HE, 40X.

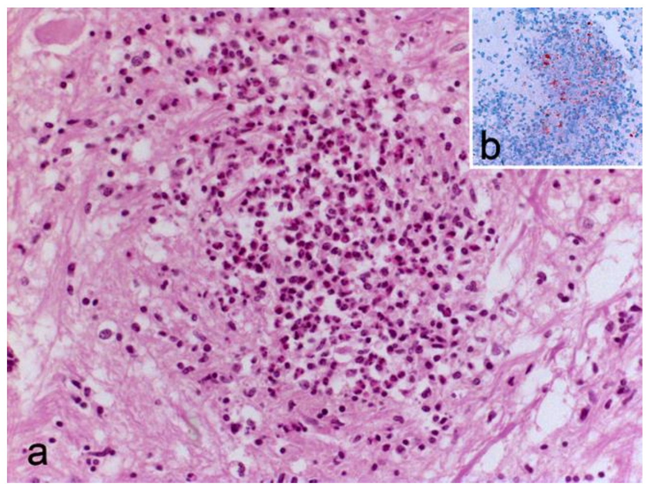

Figure 5. Bovine, midbrain, histopathologic changes consistent with infection by *Listeria monocytogenes*. (a) Microabscess in neuropil of brainstem. HE, 40X. (b) Multifocal intra and extracellular positive immunostaining anti-*Listeria monocytogenes* in microabscess. IHC, 20X.

Six cattle had severe multifocal to coalescing granulomatous meningoencephalitis, more evident in the cerebrum (Fig. 6). In one of the cases, the lesion affected cerebrum, cerebellum, brainstem, trigeminal ganglion, and rostral epidural *rete mirabile*. These samples were submitted to Ziehl-Nielsen staining, which demonstrated intralesional acid-fast bacilli (Fig. 6C). Histopathological and histochemical findings were consistent with infection by *Mycobacterium* sp., allowing the conclusive diagnosis of cerebral tuberculosis. Although the prevalence of the disease in Brazil is not quite known, there are previous reports of *Mycobacterium*-associated neural lesions in cattle in the State of Minas Gerais (3, 7, 19). Therefore, tuberculosis should be considered in the differential diagnosis of granulomatous neurological lesions.

Nine cattle had significant CNS circulatory changes, which were most evident in the cerebral cortex. These lesions were characterized by an intense and diffuse hyperemia with or without multifocal hemorrhages. Numerous intra-erythrocytic structures of approximately 2 µm in diameter, with morphology compatible with *Babesia bovis* were visualized inside blood vessels in cortex. Circulatory changes were the only significant lesion observed in these cases of cattle with neurological signs, therefore, the presumptive diagnosis of cerebral babesiosis was established. Entrapment of erythrocytes infected with *B. bovis* in capillaries and venules in the brain, particularly in the cortex is a highly significant diagnostic finding. Grossly, in these cases usually the fresh (not fixed) cerebral cortex has a cherry pink color (1, 8, 40).

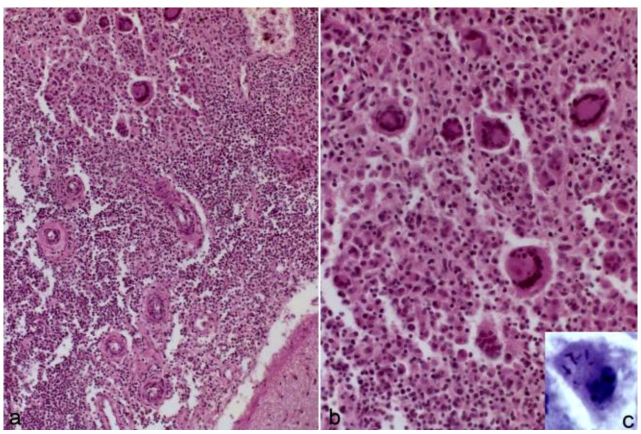

Figure 6. Bovine, brain, microscopic alterations compatible with brain tuberculosis. (a) Diffuse granulomatous meningoencephalitis. HE, 20X (b). Granulomatous reaction characterized by numerous Langerhans giant cells associated with lymphocytic infiltrate and fibrous connective tissue proliferation. HE, 40X. (**c**) Multinucleated giant cells type Langhans containing bacteria. Ziehl-Nielsen, 100X.

Corroborating previous studies (16, 42), the absence of significant histopathologic changes were observed in most of the samples (60.18% - 591/982). This result may reflect sampling of cattle affected by neurologic diseases that do not induce CNS lesion. Another important factor that favors this high frequency of samples without conclusive diagnosis is insufficient sampling, which may not provide suitable segments of the CNS. Numerous artifacts associated with autolysis were observed in 10.29% (101/982) of the cattle. Therefore, autolysis may have had an important impact in the present study, preventing an appropriate histopathologic assessment.

Animal health centers in Brazil provide routine diagnosis for rabies in cattle (32). In this study, the histopathologic evaluation of CNS samples of cattle negative for rabies led to the identification of histopathologic changes in 30% of the cases, and also allowed to establish an etiologic diagnosis in 7.4% of the cases. Histopathologic analysis allowed the differential diagnosis of infectious causes of neurological diseases in cattle. This practice should be encouraged, since it may generate additional epidemiological information, and aid define effective measures of prevention, control or eradication, contributing significantly to improvement of animal health protection actions in the State of Minas Gerais.

Conclusion

Several neurological diseases, other than rabies, were diagnosed in the State of Minas Gerais. Histopathologic analyses provided a conclusive diagnosis 7.4% (73/982) of the cases.

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