



Review article

Polioencephalomalacia in ruminants in Brazil

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Corresponding author: Claudio S.L. Barros, Departamento de Patologia, UFSM, 97105-900, Santa Maria, RS, Brazil.Email: claudioslbarros@uol.com.brSubmitted January 21st 2010, Accepted March 15th 2010**Abstract**

Polioencephalomalacia (PEM) of ruminants is a complex disease. The term indicates a morphological diagnosis where severe cortical neuronal necrosis results in softening of cerebral grey matter. Initially though as a single disease caused by thiamine deficiency, it is currently believed that PEM is caused by different etiological agents through different pathogenic mechanisms or through a single pathogenic mechanism triggered by different agents. In this paper the putative cases and pathogenesis of PEM in ruminants are critically reviewed and discussed. Also reviewed are the epidemiology, clinical signs, gross and histological findings and methods of diagnosis of cases of PEM described in ruminants in Brazil

Key Words: Diseases of cattle, neuropathology, polioencephalomalacia**Introduction**

Polioencephalomalacia (PEM) is a descriptive morphologic term used to describe the necrosis with softening (malacia) of the grey matter (polio) of the brain. Cerebrocortical necrosis is used in Europe, especially in United Kingdom (18, 38, 56) as a synonymous. The use of the term "polioencephalomalacia" has caused some confusion over the years. It was originally applied to designate a specific disease of cattle and sheep reported from Colorado, USA, presumably caused for thiamine deficiency and characterized by malacia of the telencephalic cortex (39). Since then, the term has been used not as solely as a morphologic diagnosis but rather to designate a specific disease of ruminants, characterized by cerebrocortical malacia and caused by thiamine deficiency. However, it is currently known that many cases of PEM in ruminants can not be ascribed to thiamine deficiency and many others causes came to be implicated in the development of this morphologic lesion in ruminants (Table 1). In Brazil, PEM has been used to indicate specific diseases, the etiology of which for the most part, has been elucidated or properly investigated. Actually we do not even know, if all cases described as PEM are the same disease or if different diseases bearing the same lesion are described under the same appellation (2, 47).

PEM is described as a neurological non-infectious disease which affect cattle (2, 80), sheep (48, 80), goats (10, 48, 80) and buffaloes (80). The disease presents worldwide distribution and is responsible for important economic losses in various countries.

As stated above, for a long time PEM was considered a disorder caused by thiamine (vitamin B1) deficiency. The onset of the condition was generally associated with certain dietary conditions, such as high quantities of grains or inadequate roughage (34, 80) and transfer of animals from poor range forage to other lush green pastures (39). Although this epidemiological facts still hold, the participation of the thiamine in the pathogenesis of the PEM has been questioned, for there was no changes in the concentrations of thiamine in ruminal fluid, tissues or blood of cattle and sheep coming down with the disease (25, 52, 62, 90, 91). Conversely, severe thiamine deficiency experimentally induced in sheep failed to brought up PEM (68). Conversely, thiamine activities such as thiamine dependent erythrocyte transketolase and alimentary thiaminases can be altered in other ruminant pathological conditions (50, 52).

From 1956 up to the current days many researchers observed that PEM can have several causes in ruminants, including sulfur poisoning (13, 27, 28, 43, 53), salt poisoning associated to water privation (49, 96, 102), lead poisoning (9, 42, 45, 77, 101), ingestion of levamisole and tiabendazole (50), or of

thiamine analogues such as amprolium (51, 57, 64, 94), ingestion of animal cadavers (79), ingestion of molasses – probably high in sulfur (62), and abrupt change from poor forage to lush green pastures (65). The ingestion of plants rich in thiaminases (78, 82), the peracute poisoning by *Phalaris* spp. (1) and the infection by bovine herpesvirus (6, 7) are other

reported causes for PEM. Acute laminar necrosis of the brain cortex has also been associated with poisonings by cyanide or monofluoroacetic acid, or by plants that contain these substances (47).

Table 1. Reported causes of polioencephalomalacia in ruminants.

Cause	Reference
Deficiency of thiamine	39, 80
Sulfur poisoning	13, 27, 28, 43, 53, 76, 100
Lead poisoning	9, 42, 45, 77, 101
Salt poisoning (water deprivation)	44, 49, 96, 102
Infection by BoHV	6, 7, 11, 19, 88, 89
Peracute poisoning by <i>Phalaris</i> spp.	1
Ingestion of molasses (probably high in sulfur)	62
Abrupt change of poor range forage for other of excellent quality	65
Administration of levamisole and tiabendazole	50
Administration of amprolium	51, 57, 64, 94
Ingestion of thiaminase rich plants	78, 82
Ingestion of animal cadavers	79

The disease in Brazil

Etiology

Thiamine deficiency has been suggested as the cause in some outbreaks of PEM of occurring in ruminants in Brazil. Goats which consumed the fruits of *Hovenia dulcis* (popularly known in Brazil as “uva-do-Japão”) for five days developed PEM (10). *H. dulcis* is rich in carbohydrates (36), and it is believed that these goats have developed thiamine deficiency secondary to ruminal acidosis. Thiamine deficiency is suspected to be the cause of PEM in cattle that went through abrupt change from poor to excellent quality of forage (65) or ingested cadavers left in the field and which contained thiaminase-rich clostridia (79). However the role of thiamine in these cases was not proven by laboratory determination of thiamine levels in tissues or body fluids.

Sulfur toxicosis has been also associated with PEM in Brazil at least in three opportunities. In one instance (48) 10 outbreaks of PEM were described in sheep and goats from Northeastern Brazil. In 9 outbreaks the cause of the disease was not determined, but in one of them it was probably due to sulfur toxicosis caused by the consumption of a high sulfur energy-protein-mineral mixture containing 1.3% of sulfur flower (96% sulfur) and 30% chicken litter (0.39% sulfur). Two outbreaks of PEM in cattle reported from Southern Brazil are attributed to sulfur toxicosis. In one of them (100) 2 out of 35 Holstein cows that consumed ration to which sulfur was added succumbed to PEM. Although the exact amount of sulfur added to the ration was not determined, epidemiological evidence indicates sulfur toxicosis in this outbreak. The other outbreak involved one lot of 30 calves from which 6 (20%) died (13). The total sulfur

intake of these calves was 0.38% dry matter (forage, water, ration and mineral supplementation) and the values of ruminal sulfide concentration ranged from 1,000 to 2,500ppm. Other etiologies such as infection by bovine herpesvirus (negative PCR) and lead poisoning (lead not detected) were ruled out (13).

There is one outbreak of PEM associated to salt poisoning and water deprivation reported in cattle in Brazil (44), but some Brazilian researchers believe that the common practice of Brazilian farmers to feed cattle with mineral salt or supplements rich in energy and protein could be involved in inadequate and excessive consumption of sodium, mainly by beef cattle (86).

Cases of bovine PEM caused by lead poisoning have been reported in cattle from the Brazilian states of Santa Catarina, Paraná (16), Rio Grande do Sul (101) and Mato Grosso do Sul (45). Cattle, specially calves, are the domestic species more frequently affected by lead poisoning (3). Usually, the cases are associated with exposure of herds to battery residues, paints, lubricants, machine oils, industry fume, weedkillers or insecticides (8, 45, 101).

Infection in cattle by bovine herpesvirus (BoHV) is another cause of PEM reported from several regions of Brazil (11, 19, 83, 87, 88, 104). This contagious disease affects mainly young cattle that had experienced stress situations. Clinical signs and lesions are similar those observed in traditional PEM, however cerebral non-suppurative inflammatory lesions with occasional intranuclear inclusion body in neurons and glial cells predominate in BoHV infected cattle. Recently, two subtypes of virus (BoHV-1 and BoHV-5) have been detected in field cases of meningoencephalitis in Southern Brazil (89). In the state of Mato Grosso do Sul, Midwestern Brazil, outbreaks of meningoencephalitis by BoHV-5 and PEM

share epidemiological feature and it was suggested (14) that the BoHV-5 meningoencephalitis could be associated with reactivation of a latent viral infection, during the development of PEM. In one experimental study (14) the simultaneous production of PEM and diffuse meningoencephalitis, with isolation of BoHV-5, in one steer treated with ammonium sulphate, 118 days after BoHV-5 inoculation, suggests that latent BoHV-5 was reactivated in this animal submitted to experimental induction of PEM. If this hypothesis becomes fully demonstrated, it will raise a problem in differential diagnosis in ruminant neuropathology in Brazil since it is an accepted rule of thumb that conventional PEM could be differentiate form BoHV-5 meningoencephalitis on the bases of inflammatory response, abundant in the latter and absent or very mild in the former.

Epidemiology

PEM was described in cattle in the Brazilian states of Rio Grande do Sul (13, 67, 85, 92, 93, 95, 97, 101), Minas Gerais (20, 65), Pernambuco (103), Mato Grosso do Sul, São Paulo (22, 46, 69, 79, 93), Paraíba, Pará (47), Mato Grosso and Goiás (30, 46, 63, 93). Outbreaks of PEM in sheep are reported from the Northeastern states of Pernambuco (70, 103) and Paraíba (48) and from the Midwestern (66). There are two outbreaks of the disease reported in goats in Brazil: one in the Northeastern state of Paraíba (48) and another in the Southern state of Rio Grande do Sul (10). One report describes PEM in young buffaloes in the Midwestern state of Mato Grosso do Sul (31). Epidemiologic or environmental features related the occurrence of PEM were described in certain geographic regions, such as United States (4, 29), New Zealand (35) and Australia (61). However, similar studies are scarce in Brazil. PEM represents 0.1 and 4.4% of all central nervous diseases diagnosed in cattle in Rio Grande do Sul (92) and Mato Grosso do Sul (73), respectively. There are too few reports of the disease in small ruminants that could allow for similar data in Brazil but in other countries approximately 20% of all deaths in feedlot sheep are related to PEM (80). In Brazil, outbreaks of PEM are reported in small ruminants raised intensively (48, 103) or, less frequently, in small ruminants raised at pasture (48).

The disease can occur as outbreaks with several animals affected (43, 65, 69) or as isolated cases (20, 46) and, by and large, does not present seasonality (46, 48, 69, 93, 103), although, outbreaks of PEM are reported in Mato Grosso do Sul mainly in the dry period (July to September) (79).

Morbidity, mortality and lethality rates are respectively 0.04-14%, 0.04-14% and 43-100% (46, 86, 93). Lethality rate can be lower when animals are treated in the beginning of the disease. Apparent there is no preference for sex or breed in cattle (93) but Merino sheep appear to be much more resistant than other breeds (58). When PEM is associated to sulfur toxicosis (15, 32, 35, 38) or salt poisoning with water deprivation (49, 102), the mortality rate can be higher.

It demonstrates that the specific cause interferes with the epidemiology of the disorder.

Although international literature mentions that PEM cases occur mainly in young cattle raised at feedlot, especially in United States, United Kingdom, Australia and New Zealand (33, 39, 24, 72, 80), in Brazil and Uruguay cases of PEM are observed more commonly in adult cattle raised at pasture (20, 30, 63, 65, 67, 69, 79, 86, 93, 103) indicating that different factors play a role in the etiology and/or pathogenesis of the disease in this part of the world.

Clinical signs

Clinical signs observed in PEM-affected ruminants are reflexes of the primary lesions of the telencephalon, and also the secondary lesions in the cerebellum and brainstem. These latter changes results of compression of cerebellum and brainstem by an edematous swollen telencephalon (84). The main clinical signs are central blindness, lethargy, separation from the herd, incoordination, muscle tremors, ataxia, intermittent grinding of teeth, drooling, opisthotonus, nystagmus, strabismus, seizures, reduced tonus of the tongue, recumbence and paddling movements. Blindness is one of the most consistent signs in PEM. In one study on the natural disease carried out in cattle in the Southeastern Brazilian state of São Paulo, each affected cattle was blind (22). In the outset of the clinical course, the animals may be excited and aggressive (86). Average clinical course is 2-4 days (93), but acute courses as short as 12 hours (69, 93) or chronic as long as 22 days in sheep (103) or 25 days in cattle (22) are described.

Sulfur toxicosis associated-PEM has two forms of clinical presentation. An acute form includes blindness, seizures, opisthotonus, head pressing, recumbence and, frequently, death. Alternatively, a subacute form is usually followed by recovery with mild nervous deficits or, on occasion, it is followed by a more severe disease course with recumbence and seizures (28). Generally, the clinical signs occur from the third to eight week of exposure to sulfur (23, 35, 75). An important clinical finding in sulfur toxicosis associated-PEM is the significant trodden egg odor exhaling from the poisoned animal. This finding can be felt also during gross evaluation of the rumen (4, 80) and it is due to the excessive ruminal production of H₂S (28).

Usually, cattle poisoned by salt develop clinical signs after prolonged period of water deprivation or restriction, followed by an unrestricted access to water. Morbidity can be high. Clinical signs which last approximately one day (8) are similar to those described in PEM resulting from other causes (99), but clinical signs also include vomiting, rumen atony, diarrhea and colic. Digestive signs are observed mainly in the direct poisoning by NaCl (58). A brown or red discoloration of serum and urine are useful indicatives of salt poisoning in cattle (8).

Neurological signs in cattle poisoned by lead are similar to those reported for PEM from other

causes. Clinical courses can be peracute with death occurring few hours after the onset of clinical signs (99), acute or subacute (2-7 days) (45, 101) or rarely a chronic course in which animals survive for longer periods (10-30 days) (9). Sudden death can be the presentation of the peracute form of the disease and in the acute and subacute form there is ataxia, muscle fasciculation, hyperesthesia, depression, central blindness, drooling, head pressing and aimless walking, circling, rumen atony, colic and fetid diarrhea (8, 99).

Gross and histopathological changes

Gross changes vary according to the severity and duration of the clinical course. In acute cases findings can be absent (67, 69, 97) or be restricted to brain swelling that need careful observation to be detected. A clear gross evidence of edema in the brain is cerebellar protrusion into the occipital foramen. Occipital telencephalon can also be displaced caudally underneath the cerebellar tentorium (subtentorial herniation). In more advanced cases the telencephalic cortex displays more characteristic changes such as flattening of gyri, yellow discoloration, softening with gelatinous or depressed areas, and cavitations filled by yellow liquid; hemorrhagic foci in the meningeal and subcortical regions are also observed (58, 65). These changes occur specifically in the gray matter of the brain and are better detected on the cut surface of coronal sections. More affected areas correspond to dorsal cortex, and are more pronounced in the sulci (46, 69). The lesions typically fluoresce under ultraviolet light (365 nm wave length) (37); fluorescent material being variable identified as lipid metabolites within macrophages or high-molecular-weight collagen-like substance (58). In chronic cases, cortical width can markedly decrease or the cortical tissue can disappear in altogether. In sulfur-associated PEM, the ruminal fluid can be thick and dark (60).

Histologically, in the acute cases there is segmentar laminar necrosis of cortical telencephalic neurons (red neurons). This lesion is characterized by shrunk and eosinophilic cytoplasm, chromatolysis and nuclear picnosis. This type of neuronal change should not be mistaken by the the black or dark-blue so called "dark neurons", that are artifacts due to excessive postmortem manipulation of the brain (5, 40). Edema is a common change and consists of augmentation of the perineuronal and perivascular spaces with multiples vacuoles in the neuropil (spongiosis). With time the spongiosis evolves in some cases to form crevices between laminar neuronal layers or between the gray and white matter (2, 93). Ultrastructural study showed that spongiosis and the increase of the perineuronal and perivascular spaces correspond to astrocytic edema (64). In the sulfur toxicosis, spongiosis can affect the deep layers of cortical neurons and extend to the adjacent white matter (28). Neuronal necrosis is reportedly more severe in the deeper neuronal layers (58); however in a study carried out on natural cases of PEM in cattle, the red neurons and edema predominated

in the extern and intern granular cortical layers (93). There is hypertrophy of the endothelial cells nuclei in vessels adjacent to the affected areas. Mild infiltration of mononuclear or, occasionally polymorphonuclear cells, can be observed (69, 93). In subacute or chronic cases, there is necrosis of neuroectodermic components and infiltration of large foamy macrophages known by the sobriquet of *gitter cells*. Loss of telencephalic cortex with formation of a cystic area between the white matter and the leptomeninges (residual lesion) can occur in some cases (65). Similar change is observed in advanced cases of meningoencephalitis by BoHV (88).

In addition, in some cases of PEM, can occur malacia and edema down in deep structures of the brain, such as midbrain, thalamus, basal nuclei and hippocampus (93). These lesions have been described in PEM associated to sulfur poisoning (32, 38, 53, 55, 59,) and may result from compression caused by edema. Focal hemorrhages in thalamus and midbrain occur secondarily the degeneration of veins and venules (53) and fibrinoid necrosis of small arterioles (32, 35) occur in cattle naturally poisoned by sulfur. These changes are considered a more severe form of the disease associated to excessive consumption of sulfur (28). Some authors consider that in cases of PEM with cortical neuronal necrosis associated with lesions in ventral structures of the brain, sulfur toxicosis is considered a probable etiology (38, 55). The morphology and topography of these lesions may distinguish sulphate induced PEM from those cases associated with thiamine deficiency (38). However similar alterations to those reported for sulfur toxicosis were observed in the brain of sheep affected by PEM experimentally induced by amprolium toxicosis (94). In these cases, the hemorrhages are more severe in the areas affected by malacia of the brain (94). Usually, cerebellar malacia are secondary to compression exerted by bony structures on the herniated cerebellum (48, 58). Alzheimer type II astrocytes were observed adjacent to neuronal necrosis and spongiosis of the neuropil in natural cases of PEM in cattle (93). Although these cells are classically encountered in hepatic or renal encephalopathies (99) due to hyperammonemia and others substances (74), no explanation for the occurrence of such cells in cases of PEM in cattle was put forward.

Gross findings of salt poisoning are characterized by subdural hemorrhages (96), congestion of meningeal blood vessels or softening of cortical caudal brain. In addition to the laminar neuronal necrosis, in some cases of salt poisoning there is accumulation of eosinophils in the Virchow-Robin spaces, in submeningeal regions and, less frequently, in neuropil (44).

CNS lesions in cattle poisoned by lead are described for the acute, subacute and chronic forms of the poisoning (58). The gross findings in the brain of these cattle can be either absent in peracute or acute cases (45) or similar to those reported in PEM due to other causes (101). There are several reports on lead poisoning stating that malacia occur preferentially in the top cerebral gyri (9, 42, 45, 98) and that the lesions

are more severe in the occipital telencephalic lobes in cattle with acute clinical courses and in the brain stem and telencephalic cortex in cattle with more protracted clinical courses (9). A frequent finding in cattle poisoned by lead is degeneration of the renal tubular epithelium associated with acid-fast intranuclear eosinophilic inclusion bodies (98, 101). In the brain, in addition to the typical lesions of PEM, vasculitis can be observed (8).

PEM can also be a manifestation of the BoHV induced meningoencephalitis in cattle. However in the BoHV induced PEM the gross changes of cortical malacia occur mainly in the frontal telencephalon and the histological lesions includes well developed mononuclear perivascular cuffs in many regions of the brain and, in a variable proportion of the cases, characteristic basophilic intranuclear inclusion bodies are observed in astrocytes and neurons (88, 89).

Diagnosis

The diagnosis of PEM is based in the epidemiologic, clinical, gross and histopathological findings. An useful finding for the diagnosis of the disease consists in visualization of fluorescence of affected areas of the brain (mainly telencephalic cortex) under UV light (13, 22, 37). Also, a therapeutical diagnosis can be achieved following the recovery of cattle treated with thiamine and corticoids (69). However, other neurologic diseases of the central nervous system of ruminants can respond favorably to treatment with thiamine (12).

Serum biochemistry presents inconsistent results and contribute little for the diagnosis of the disease (76). However increase of piruvate, lactate, oxoglutarate and thiamine pirophosphate (TPP) activity are described in PEM associated to thiamine deficiency (80, 81). TPP activity varies from 30 to 50% in healthy cattle and sheep. In PEM cases, this rate be up to 70-80% (80). Serum concentrations of urea and creatinine can be moderately increased in some cases and the activities of aspartate aminotransferase and creatine phosphokinase are substantially increased in severely affected animals (76). Cerebrospinal fluid (CSF) analysis can reveal mild elevation of protein content and of the numbers of mononuclear cells, which can be vacuolated. These CSF changes also occur in PEM caused by lead poisoning (8).

In suspected cases of sulfur poisoning, the mineral should be investigated in the water, ration, pasture or mineral supplementation available to the animals (86). Maximum sulfur concentration allowed in the diet is 0.4 % dry matter basis (71). Other useful form of confirm the diagnosis is to detect elevated concentrations of hydrogen sulfide (H_2S) in the rumen gas cap of affected animals (13, 26). Water sulfur content greater than 1,000 ppm, dietary sulfur greater than 4,000 ppm, or ruminal gas H_2S greater than 1,000 ppm are considered suggestive of toxicosis (8). Ruminal H_2S levels over 2,000 ppm can precede the development of PEM (26). In addition the rate of blood sulfhemoglobin can give an estimation of the ruminal

absorption of sulfide, but sulfhemoglobin is not detected in some cases of dietetic excess of sulfur (26).

In PEM associated to salt poisoning and water deprivation, the determination of sodium concentrations in the CSF is necessary. Sodium rates greater than 160 mEq/L are suggestive of salt poisoning in cattle (54) and sheep (41). History of excessive consumption of mineral salt and water deprivation for many days are very important epidemiological data for the diagnosis. Furthermore, hemolysis and hemoglobinuria are useful for distinguishing this condition of other CNS disorders.

In the cases of lead poisoning, the blood concentrations of this metal is a good indicator for a clinical diagnosis (17, 80). Reference lead blood values vary from 0.05-0.25 ppm; 0.35 ppm indicates poisoning and concentrations greater than 1 ppm cause death (80). This test however is not recommended by some authors as the only form of clinical diagnosis, mainly in isolated cases because lead concentrations can vary according to the stages of disease (99). Others hematologic changes include regenerative anemia and increase of the concentration of blood erythrocyte porphyrin (9). Lead can be detected also in urine and feces (99). Morphologically, there are some aspects that differentiate lead poisoning induced PEM from PEM due to other causes. In the former, cerebellar herniation almost never occurs and, edema is less severe, and the chronic lesions are also less marked with few red neurons and moderate numbers of foamy macrophages. Reportedly, the neuronal necrosis caused by lead poisoning occurs preferentially in top of the cerebrum gyri (9, 42, 45, 98). To confirm the diagnosis, it is necessary to detect the source of lead and to quantify lead residues in blood, liver and kidney. Amounts as 10 ppm in liver or kidney samples confirm the diagnosis (86). Lead accumulates in the body and can be detected in blood samples months after the ingestion (21). Differential diagnosis of PEM should include other CNS diseases of ruminants.

Final considerations

Although PEM has been diagnosed in Brazil for many decades and many epidemiologic and pathologic aspects are well recognized, the pathogenesis and the specific causes of the disease in the country have been only recently investigated and for the most part of cases of PEM reported in the country the etiology is still elusive. Continuous and systematic studies in the various regions of the country where the disease occurs are necessary to determinate the cause, pathogenesis and methods of control for the disease.

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