Cerebral and Brainstem Diseases of Cattle: Diagnosis and Review of Causes

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Introduction

Cerebral and brainstem diseases cause a change in the mental status of the affected animal. Clinical signs suggestive of cerebral or brainstem diseases are commonly seen in cattle.[1] There are more than 120 diseases that are reported to affect cerebral and/or brainstem function resulting in either coma, severe depression or seizure.[2] The scope of this paper is not to review all the causes of cerebral-brainstem disease in cattle. The intent is to provide information on how the clinical exam can be used to localize dysfunction to these areas and to review recent (since 1990) information regarding some of the diseases of cattle which affect the cerebral cortex or brainstem. The methodology for collecting cerebrospinal fluid (CSF) from cattle and the diagnostic implications that can be derived from the CSF analysis will be presented. Most diseases of the brain in cattle are caused by infectious, toxic or metabolic causes and have been so divided in the following review.

Clinical Signs

Behavioral changes and central blindness are the characteristic clinical signs of cerebral dysfunction.[1] The behavioral changes may vary from coma or stupor to belligerence and seizures. Cattle with cerebral disease are often found circling (usually towards the side of the lesion) and/or head pressing. Central blindness can be determined by absence of a menace response with normal pupillary response to light or by observation of the animal as it moves into or around objects. If only one cerebral hemisphere is affected, blindness would appear in the contralateral eye. Ataxia is absent or minimal with cerebral disease alone, although many cattle with cerebral dysfunction walk with a short shuffling gait. Opisthotonus is a common finding with severe cerebral swelling.

Depression, ataxia, paresis, and signs indicative of one or more cranial nerve deficits are characteristic findings of brainstem dysfunction. It the brainstem disease is unilateral, ipsilateral ataxia and weakness with ipsilateral cranial nerve deficits[4-12] are usually seen. If the disease is in most rostral area of the brainstem, ataxia and paresis may occur on the contralateral side.

Infectious Causes

Infectious causes of particular importance to dairy practitioners include: bacterial meningitis of calves, rabies, thromboembolic meningoencephalitis, malignant catarrhal fever, herpes encephalitis and listeriosis.

Bacterial meningitis is most common in calves 2-14 days of age[3] (mean age of 5 or 6 days).[3,4] Although inconsistently found, arthritis, omphalophlebitis or uveitis may be concurrent clinical problems.[3,4] *E. coli* is the predominant pathogen causing meningitis in calves. The pathogenic organisms are believed to most often enter via the respiratory or gastrointestinal systems or by way of the umbilicus. Bacteremia ensues, particularly in those calves with inadequate colostral antibody.[4] The least understood step in the pathogenesis of meningitis is the mechanism by which bacteria penetrate the blood-brain barrier and gain entry into the cerebrospinal fluid. Bacterial piliation appears to be a virulence factor in this step, especially for *E.coli.*[5] Once bacteria reach the cerebrospinal fluid they are likely to survive because of the absence of immunoglobulin and complement in the cerebrospinal fluid. Inflammation and tissue destruction rapidly follows, associated with release of bacterial lipopolysaccharide, activation of cytokines, neutrophil adherence to endothelial cells, and release of toxic oxygen metabolites and other inflammatory derivatives.[5] Unless treatment is initiated early in the disease, there is little chance of survival.[4,6] There is evidence that an increasing number of bacteria causing meningitis are resistant to trimethoprim-sulfa drugs.[4] Treatment with extralabel doses of Ceftiofur would seem most appropriate. Corticosteroid treatment may be beneficial if it is used early in the course of the disease (first 24 hours only).[5]

Hemophilus somnus is another bacteria that may

cause acute meningitis in older calves (usually >4 months of age for the encephalitic form).[7] The acute disease is characterized by fibrinopurulent meningitis, multifocal parenchymal necrosis with hemorrhage and thrombotic vasculitis. Calves that die with a more chronic disease process may have abscessation and cavitation of the brain.[8] The clinical syndrome in dairy replacement heifers may differ slightly from that commonly seen in feedlot animals. The disease is most common in fall and winter and may cause severe clinical signs in a single or small number of replacement heifers. The neurologic signs may or may not be preceded by respiratory signs. The brain, spinal cord, lungs, heart, joints and larynx may be affected in some calves.[7]

There has been increasing concern recently about rabies in cattle in the mid-Atlantic and the northeastern states.[9] There were 184 reported cases of rabies in cattle in the U.S. in 1992. These increasing numbers have been caused by the epizootic spread of the raccoon variant of the virus in the southeast, northeast, and central parts of the U.S. There are several species-related variants of the virus in the U.S., each with different epitopes and nucleotide sequences.[10] The susceptibility to rabies is likely related to: the infecting strain, the host's genetic background, concentration of nicotinic acetylcholic receptors in skeletal muscle, size of the innoculum, degree of innervation at the site of the bite and proximity to the nervous system.[10] Cattle may manifest either the paralytic, dumb, or furious form of the disease. The variety in form may possibly be related to the distribution of the virus in the nervous tissue.[11] An excellent review of rabies, including methods of prevention, risks, and treatment recommendations after exposure has recently been published[10] and veterinarians practicing in rabies endemic areas are encouraged to keep a copy of the article on file.

An encephalitogenic form of bovine herpes virus 1 (BHV 1) may cause encephalitis in young cattle. This neurovirulent strain of BHV 1 can be distinguished from the respiratory and genital tract isolates by restriction endonuclease analysis of the viral DNA.[12] This strain of the virus has been termed BHV 1 subtype 3.[13] It generally causes encephalitic signs and fever in young calves <6 weeks of age that are unprotected by passively acquired colostral antibodies against BHV 1 (BHV 1 antibody may be protective against the different subtypes of the virus). Respiratory signs and conjunctivitis may precede the encephalitic signs by 9-11 days. The transmission of the virus to the cerebral cortex is thought to be via the facial nerve. The attack rate has been reported to be 15-37%,[12] although an isolated case has been documented.[14] Intranuclear inclusion bodies and positive immunoperoxidase staining of the cerebral cortex can usually be found with the BHV 1 subtype 3 infection.[15] The disease is usually fatal in calves.

Malignant catarrhal fever (MCF) causes encephalitis, lymphoid necrosis and vasculitis in cattle. In the U.S. the disease is usually seen in cattle that are exposed to sheep (most commonly lambing ewes) and the disease has been termed "sheep-associated MCF." There is evidence that the sheep associated MCF virus is caused by a gamma-herpes virus which is very closely related to the wildebeast associated MCF herpes virus.[16,17] Cattle infected with sheep associated MCF will seroconvert to this gamma-herpes virus.[16,17] The clinical disease is usually sporadic in cattle, often causing severe clinical disease in only one animal in the herd. This may be a result of the low infectivity of the virus.[17,18] There are reports of outbreaks of the disease with many cases having only mild clinical signs.[19] Cattle may recover from even the severe clinical form of the disease.[19]

Bovine spongiform encephalopathy (BSE) has occurred as an epidemic in cattle in Great Britain. The disease is caused by a prion protein transmitted to cattle via ingestion of the scrapie-like agent in feeds containing meat and bone meal.[20] The incubation period is 18 months or longer and the mean age at onset of clinical signs is 60-62 months.[21] The neurologic signs most frequently reported include aggressiveness, apprehension, hyperesthesia, persistent licking, and ataxia.[22] These signs are similar to those that might occur with nervous ketosis and a variety of poisons. The potential risk of BSE occurring in the U.S. has been extensively investigated.[23] The risk of and/or the presence of the disease in the U.S. could not be eliminated.[23] A decline in the number of sheep carcasses used in meat and bone meal, the absence of sheep products in milk replacers, the failure to identify cases in surveillance of U.S. cattle imported from Great Britain and Ireland or in the pathologic review of hundreds of cattle with nervous signs, along with widespread dissemination of information about the disease to appropriate professionals would cumulatively suggest that the disease probably does not exist in the U.S. and the risk of it occurring is low.[23]

The most common disease specifically affecting the brainstem of cattle is listeriosis. Listeriosis is caused by *Listeria monocytogenes*, a facultative intracellular organism which may produce multiple abscesses in the brainstem of susceptible cows. Improperly fermented silage (pH >5.5) and soil contaminated silage are the most common sources of exposure in cattle. The organism is thought to invade the oral mucosa and migrate to the brainstem via the trigeminal nerve. Abscesses in the brainstem cause vestibular signs as circling and signs of facial paralysis, jaw weakness, and in some cases bloat or regurgitation. Signs of vestibular and facial nerve dysfunction may also be caused by inner ear infections, but these are most common in calves while listeriosis is rare in young calves. Treatment of cattle acutely affected with listeriosis is often successful when

large amounts of penicillin are given to cows that are ambulatory at the initiation of the treatment. DNA amplification techniques have recently been used for specific detection of *L. monocytogenes* in CSF, brain tissue, environment and feed samples.[24] These methodologies may help in rapid identification of the source of the organism and confirmation of the disease.[24]

Toxic and metabolic encephalopathies

Metabolic causes of cerebral dysfunction include polioencephalomalacia, nervous ketosis, ruminal acidosis, vitamin A deficiency and uremic or hepatic encephalopathy. Toxic causes are numerous but include lead, salt, organophosphate and urea poisoning. Until recently polioencephalomalacia (PEM) has been equated with thiamine deficiency. Recently an association between PEM and increased ruminal sulfide concentrations has been demonstrated.[25,26] Excessive ruminal production of sulfides may occur from the ingestion of feeds or water with a high sulfur content.[25,26] Although cattle with PEM experimentally induced by sulfide have had normal blood thiamine concentrations,[25] thiamine therapy might still be beneficial but less dramatic in its effect.

Thiamine therapy has also been shown to be beneficial in treating and protecting cattle from lead poisoning.[27] In fact, thiamine was more effective than EDTA in alleviating the clinical signs in cattle chronically exposed to lead.[27] Treatment with both thiamine and EDTA would be recommended for lead poisoning in cattle. There has been a product safety concern that cattle, although clinically recovered from lead poisoning, might continue to produce milk with excessive concentration of lead. Cattle which had exhibited clinical lead poisoning 7 months earlier had increases in blood lead at freshening but did not reach detectable levels in the milk.[28] If there are shorter durations between poisoning and milk analysis and/or if greater or more persistent exposure to lead occurs there would be the possibility for prolonged contamination of the milk. The clinical signs of lead poisoning may be indistinguishable from PEM, although extreme nervousness, exaggerated chewing, frequent urination and facial fasiculations are more common with lead poisoning. The exaggerated signs may also occur with urea, chlorinated hydrocarbon, organophosphate, or ammoniated forage toxicosis.[29]

Hypernatremia (sodium chloride intoxication) seems to be more common now that most oral electrolyte solutions are hypertonic. Toxicity usually occurs from improper mixing of these oral electrolyte solutions and their subsequent administration to calves with neonatal diarrhea.[30] Affected calves usually become extremely depressed, blind and recumbent. Salt poisoning should be considered in diarrheic calves that become unexplainably depressed and recumbent after being treated by lay personnel with oral electrolytes. Severe hypoglycemia and/or acidosis could also produce identical clinical signs. Serum and CSF sodium concentrations are usually between 170-220 mEq/L.[30] Surprisingly, some calves will recover if serum sodium is gradually lowered by administering sodium containing fluids e.g. Lactate Ringers with dextrose.

Urea poisoning, vitamin A deficiency and severe ruminal acidosis are other diseases that may result in blindness and severe depression or seizure in cattle.[31,32,33] These are more likely to be found in beef cattle than in dairy cattle. The use of activated charcoal in cases of severe ruminal acidosis appears promising.[33] Organophosphate poisoning, especially that caused by terbufos[34] mixed with seed corn, has been commonly seen in dairy cattle. Colic, salivation, depression, frequent urination, and acute death are common findings. Portosystemic shunts have been recently reported in three Holstein heifers.[35,36] Clinical signs did not occur until the calves were 5-8 weeks of age and were being fed increasing amounts of grain and high protein roughage. Seizure, opisthotonus, paddling, and coma may be followed by apparent recovery without treatment, only to recur in a few days. Hepatic failure from hepatic cirrhosis or obstruction of the common bile duct by an abscess may also cause fulminant neurologic signs in cattle. Hepatic enzymes will be increased in the serum of cattle with cirrhosis or biliary obstruction but not in calves with portosystemic shunts. Trauma to the head might also cause severe depression in cattle; complete recovery might occur with supportive therapy. Tumors of the brain are rare in cattle but do occur including the sporadic form of lymphosarcoma.[37]

Cerebrospinal fluid collection and evaluation

The most direct antemortem laboratory method of evaluating the central nervous system is the examination of CSF. The normal bovine CSF is clear, contains no erythrocytes, <6 white blood cells/ul (a mixture of lymphocytes and macrophages), and has a protein content of < 60mg/dl.[6] The CSF can be collected from either the atlanto-occipital or lumbosacral (LS) sites. A three and one-half inch needle is usually sufficient for the puncture, even in adult cows. The LS procedure is more difficult in recumbent adults but can be accomplished easily in recumbent calves if the hips are flexed and the pelvic limbs are extended alongside the abdomen. Contamination of the CSF with erythrocytes is also more likely to occur with lumbosacral collection than with atlanto-occipital collection.[6]

The total leukocyte count of the CSF has been shown to be useful in separating septic causes from metabolic, or toxic disorders.[6] Cattle with acute bacte-

rial infections of the CNS usually have a neutrophilic pleocytosis. As the infection becomes more chronic, macrophages may predominate and in brain abscesses neutrophils may be relatively few.[6] Bacterial meningitis typically causes higher numbers of erythrocytes and greater discoloration of the CSF than with any other disease except acute truma.[6] Listeriosis causes a pleocytosis with the majority of the cells being macrophages.[6]

Viral meningoencephalitis tends to produce a predominatly lymphocytic pleocytosis. Rabies may produce the least cellular response of any septic condition.

Cattle with acute trauma and cerebral cortical signs have increases in CSF protein, erythrocytes and leukocytes.[6] Erythrophagocytosis is usually present and can be helpful in separating prior hemorrhage from artifactual hemorrhage due to collection. Abnormal number of macrophages may also occur associated with prior hemorrhage and accompanying inflammatory reaction.[6]

Cattle with encephalopathy resulting from metabolic or toxic causes often have normal spinal fluid. Cerebrospinal fluid protein and leukocytes may be mildly increased.

Conclusions

Clinical signs suggestive of cerebral or brainstem diseases are commonly seen in cattle and there are many causes. Cerebral or brainstem dysfunction can usually be determined from the clinical exam. The exam is also important in determining if the dysfunction is bilaterally symmetrical or asymmetrical which can be important when formulating a differential diagnosis. Cerebrospinal fluid can be easily collected in standing cattle and recumbent calves and is helpful in separating infectious causes from toxic or metabolic causes. Although a neutrophilic pleocytosis is most characteristic of the bacterial infections, macrophages may be the predominant cell type with more chronic infections. Lymphocytes are usually the predominant cell in the CSF with viral diseases. The CSF is often normal with toxic or metabolic conditions.

The most common bacterial causes include bacterial meningitis in young calves, and listeriosis and thromboembolic meningoencephalitis in older replacement heifers or adults. The most common cause of bacterial meningitis in calves is *E.coli* which is often resistant to most approved drugs with the exception of ceftiofur. Cattle with listeriosis can often be successfully treated with extra-label dosages of penicillin if treatment is begun early in the disease. DNA amplification techniques can be used in the rapid identification of the source of the organism and confirmation of the disease. Viral diseases of importance may include rabies, malignant catarrhal fever, and herpes encephalitis. The number of cases of animal rabies has increased substantially in the past two years. Therefore, veterinarians should become familiar with the clinical diagnosis, risk factors that would constitute exposure, and post-exposure management. There is increasing evidence that the sheep associated MCF is caused by a gamma-herpes virus and serologic testing may be helpful in the diagnosis. Bovine spongiform encephalopathy, a neurologic disease of cattle caused by a prion, has not been reported in the U.S. The potential risk of BSE occurring in the U.S. is thought to be low but cannot be eliminated.

There are numerous toxic and metabolic causes of cerebral dysfunction in cattle but new information is available on only a few. Polioencephalomalacia has been shown, in some instances, to be associated with high sulfur diets rather than thiamine deficiency. Cattle with lead poisoning may exhibit significant clinical improvement when treated with thiamine alone and it should be used with EDTA in the treatment of lead intoxication. The incidence of salt poisoning appears to be increasing, and is most commonly associated with the feeding of improperly mixed electrolyte solutions to calves with diarrhea. Salt poisoning should be suspected in calves that become unexplainably depressed after receiving electrolyte solutions that are not properly diluted.

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Abstract

Laparoscopy through the vaginal fornix of cows for the repeated aspiration of follicular oocytes

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A simple method is described for the repeated laparoscopic examination of the internal reproductive organs of cows and heifers through the vaginal fornix. It can be performed in a simple crush in less than 15 minutes, does not require surgery and can be used under field conditions. The method has been used for aspirating oocytes from follicles which were at least 2 mm in diameter in animals under sedation and epidural anaesthesia. In a preliminary study 11 cows and eight heifers were allocated into two groups: 12 animals were treated weekly with 500 iu pregnant mare's serum gonadotrophin and seven animals were not stimulated with gonadotrophin. The mean numbers of oocytes collected from the treated cows (6·3) and heifers (3·3) did not differ significantly from the numbers collected from the stimulated cows (5·5) and heifers (4·0). After the procedure had been established a mean oocyte collection rate of up to 75 per cent of follicles aspirated was obtained in 12 unstimulated heifers. When follicles were aspirated twice instead of once a week, the mean number of follicles observed (16·2 vs 7·0) and the mean number of oocytes collected per week (12·2 vs 5·2) were significantly higher ($P<0·05$).