Seizure Disorders in 43 Cattle

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Background: Large animals have a relatively high seizure threshold, and in most cases seizures are acquired. No published case series have described this syndrome in cattle.

Objectives: To describe clinical findings and outcomes in cattle referred to the Veterinary Teaching Hospital of the University of Turin (Italy) because of seizures.

Animals: Client-owned cattle with documented evidence of seizures.

Methods: Medical records of cattle with episodes of seizures reported between January 2002 and February 2014 were reviewed. Evidence of seizures was identified based on the evaluation of seizure episodes by the referring veterinarian or 1 of the authors. Animals were recruited if physical and neurologic examinations were performed and if diagnostic laboratory test results were available.

Results: Forty-three of 49 cases fulfilled the inclusion criteria. The mean age was 8 months. Thirty-one animals were male and 12 were female. Piedmontese breed accounted for 39/43 (91%) animals. Seizures were etiologically classified as reactive in 30 patients (70%) and secondary or structural in 13 (30%). Thirty-six animals survived, 2 died naturally, and 5 were euthanized for reasons of animal welfare. The definitive cause of reactive seizures was diagnosed as hypomagnesemia (n = 2), hypocalcemia (n = 12), and hypomagnesemia-hypocalcemia (n = 16). The cause of structural seizures was diagnosed as cerebrocortical necrosis (n = 8), inflammatory diseases (n = 4), and lead (Pb) intoxication (n = 1).

Conclusion and Clinical Importance: The study results indicate that seizures largely are reported in beef cattle and that the cause can be identified and successfully treated in most cases.

Key words: Central nervous system; Bovine; Neurology; Seizures.

An epileptic seizure is the clinical manifestation of excessive and hypersynchronous abnormal neuronal activity in the cerebral cortex.[1] Neurotransmission is regulated by a balance between excitatory and inhibitory stimulation. Seizures occur when excessive excitation or loss of inhibition results in uncontrolled neuron depolarization.[2] Seizure threshold (defined as the number of neurons that must be activated to induce a seizure)[2] is higher in large and adult animals than in small and young ones.[3]

Cluster seizures are ≥2 seizures lasting <5 minutes within a 24-h period. If seizures last >5 minutes or if full recovery, between them, does not occur the condition is defined as status epilepticus. The term epilepsy generally refers to recurrent seizures of any cause.[2] Seizures in domestic animals can be classified as focal or generalized.[4,5] The etiology of seizures can be classified

as idiopathic, structural, reactive, metabolic (because of underlying systemic disorders), or unknown.[5,6]

According to the new International League Against Epilepsy (ILAE) classification, seizures are classified according to etiology as intracranial structural (when seizures are caused by intracranial structural lesions), extracranial structural (including metabolic or toxic diseases), genetic (if a gene mutation is identified as the cause of seizures) and idiopathic or unknown.[4,7]

This new classification has been adopted by many veterinary neurologists but has been met with considerable dissatisfaction from others.[5] For the purposes of this study, the former classification has been adopted.

In large animals, most cases of seizures are acquired.[3] To date, there are no published case series describing this syndrome in cattle. The aim of this retrospective study was to report the clinical findings and outcomes in cattle referred to the Veterinary Teaching Hospital of the Department of Veterinary Science of Turin (Italy) between January 2002 and February 2014 because of seizures.

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Materials and Methods

The medical records of cattle with episodes of seizures were reviewed. Evidence of seizures was identified based on evaluation of seizures by the referring veterinarian or 1 of the authors. Animals were recruited if physical and neurologic examinations were performed, the latter by a board-certified neurologist (ADA), and if diagnostic laboratory test results for the diagnosis were available. The laboratory tests included CBC and biochemical profile (aspartate aminotransferase [AST], alkaline phosphatase, blood urea nitrogen, creatinine, glucose, creatine phosphokinase [CK], total serum protein, albumin, calcium [Ca^{2+}], magnesium [Mg^{2+}] and phosphorus). Evaluation of sodium, potassium, ionized calcium (iCa^{2+}), pH, partial pressure of carbon dioxide, partial pressure of oxygen, total carbon dioxide, bicarbonate, base excess in the extracellular fluid compartment and oxygen saturation, total bile acids, cerebrospinal fluid (CSF) analysis, postmortem, and histopathologic examination were performed in selected cases. Information on follow-up and treatment outcome also were collected. Animals treated before presentation were excluded from the study.

Hypomagnesemia was considered as the cause of seizures when the serum Mg^{2+} concentration was <1.8 mg/dL (reference range, 1.8–2.4 mg/dL) and the animal responded to IV Mg^{2+} administration (Mg gluconate 5 g/100 kg, q12 hours for 3–5 days, depending on clinical response). Hypocalcemia was considered as the cause of seizures when the total serum Ca^{2+} concentration was <8.0 mg/dL (reference range, 8.0–11.4 mg/dL) or iCa^{2+} was <4.80 mg/dL (reference range, 4.80–6.40 mg/dL) and the animal responded to IV Ca^{2+} administration (Ca gluconate 20 g/100 kg, q12 hours for 3–5 days, depending on clinical response) in addition to SC vitamin D_3 supplementation (5,000,000 IU, q24 hours, once a week for 3 weeks). Hypomagnesemia and hypocalcemia were considered as the cause of the seizures when both of these conditions were present.

Cerebrocortical necrosis (CCN) was suspected in patients with neurologic signs indicating forebrain disease, normal biochemistry results, normal CSF or CSF showing slight mononuclear pleocytosis and mildly increased protein concentration.[3,8] Diagnosis was confirmed by empirical treatment with thiamine (10 mg/kg IV, q12 hours, for 5 days) to facilitate diagnosis based on positive treatment response or postmortem and histopathologic examination.[3] All laboratory tests on blood and CSF were done at the clinical pathology laboratory of the Department of Veterinary Sciences.

Venous blood samples were collected from the jugular vein and stored in EDTA tubes for hematologic analysis and in preservative-free tubes for biochemical analysis. Cerebrospinal fluid was collected from the lumbosacral site as previously described.[9] Cerebrospinal fluid analysis was performed within 1 hours after collection. Blood gas analysis was performed in the field using a portable blood gas analyzer[a] with heparinized blood samples. Postmortem and histopathologic examinations were carried out at the Istituto Zooprofilattico Sperimentale del Piemonte, Liguria e Valle d'Aosta.

Statistical Analysis

Descriptive statistics were calculated using a freeware statistical software package (R V.1.12.2).[b] Numerical data are presented as the mean ± SD, minimum and maximum. Nominal data are presented as frequency or percentage when appropriate.
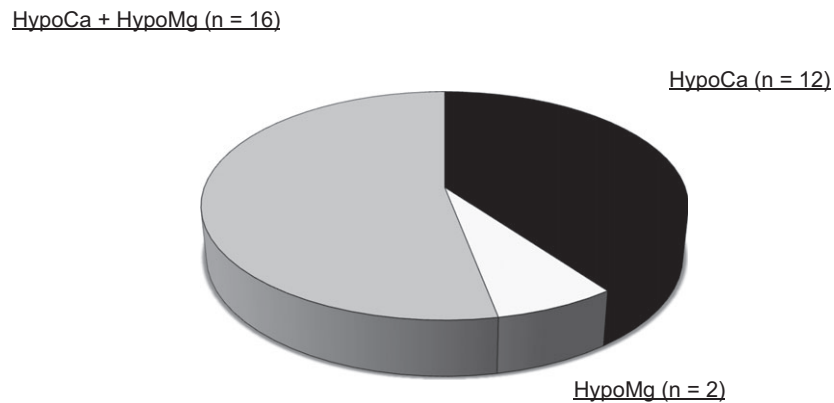
Results

Forty-three of 49 cases fulfilled the inclusion criteria. Six cases were excluded because seizures were observed only by the farmer (n = 3), animals were treated before the presentation (n = 2), or the diagnostic evaluation was incomplete (n = 1). All affected animals were referred because of an acute onset of seizures lasting from 2 to 7 days. All animals experienced multiple seizures, although establishing the exact number in each case was not possible. Three cattle exhibited cluster seizures.
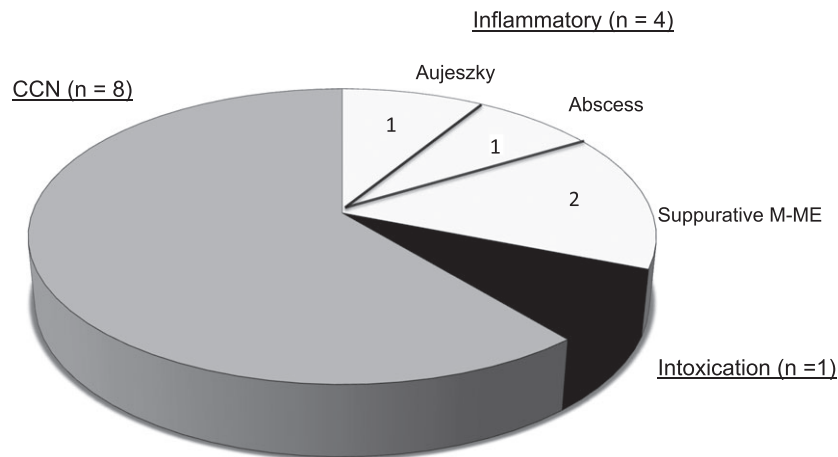
Mean age was 8 months (10 days–5 years). Thirty-one animals were male and 12 were female and came from 33 different farms. Piedmontese breed accounted for 39/43 (91%) animals. Seizures were generalized, mainly tonic-clonic, in 40 cases. Three other animals had status epilepticus at presentation. Neurologic examination, performed soon after admission, was normal in 20 cattle, whereas in 23 animals it was suggestive of forebrain (n = 19), diffuse intracranial (n = 3), or multifocal (n = 1) localization. Seizures were etiologically classified as reactive in 30 patients (70%) and secondary or structural in 13 (30%). All 20 animals with a normal neurologic examination were classified as having reactive seizures. The definitive causes of reactive and structural seizures are presented in Figures 1 and 2 respectively.

All calves in which total Ca^{2+} concentration was measured had normal serum albumin concentrations. Other biochemical abnormalities other than electrolyte abnormalities were increased serum CK (n = 15) and AST (n = 15) activities. Cerebrospinal fluid analysis was performed in 22 animals and was abnormal in 6 (reference limits: total cell counts: <10 cells/μL; microproteins: <40 mg/dL). Mononuclear pleocytosis was seen in the two calves diagnosed with CCN (total cell count: 10 cells/μL, microproteins: 50.6 mg/dL; total cell count: 30 cells/μL, microproteins: 23.3 mg/dL, respectively) and in the cow affected by Aujeszky disease (total cell count: 45 cells/μl; microproteins: 47.6 mg/dL). A neutrophilic pleocytosis was found in the two calves with a diagnosis of suppurative meningoencephalitis (total cell count: 117 cells/μl, microproteins: 272.6 mg/dL; total cell count: 33 cell/μL, microproteins: and 272.9 mg/dL respectively). Lastly, an albuminocytologic dissociation was detected in the heifer with brain abscess (total cell count: 2 cells/μL; microproteins: 48.5 mg/dL).

Thirty-six animals survived, 2 died naturally, and 5 were euthanized for reasons of animal welfare. Necropsy was performed in 6 of these 7 animals. Postmortem examination confirmed the diagnose of CCN (n = 2), Aujeszky's disease (n = 1), suppurative meningoencephalitis (n = 1), brain abscess (n = 1), and lead (Pb) intoxication (n = 1). In this last case, Pb concentration, as detected by atomic absorption spectroscopy on a pool of organs, was 96 ppm (normal values: <0.35 ppm in blood, <10 ppm in liver, <10 ppm in renal cortex). Postmortem examination was not performed in a calf with neutrophilic pleocytosis and spontaneous death. Based on the neurologic findings and CSF results, suppurative menigoencephalitis was suspected in this animal. Of the 36 survivors, 33 recovered completely (all of those with reactive seizures and 3 with CCN), whereas central blindness persisted in 3 cattle

Fig. 1. Cause of seizures classified as reactive. Serum concentrations expressed as mean ± SD. Hypocalcemia: serum Ca concentration (n = 11) and ionized fraction of Ca (n = 1) were 5.6 ± 0.8 mg/dL and iCa 2.64 mg/dL respectively. Hypomagnesemia: mean serum Mg concentration was 0.8 ± 0.3 mg/dL. Hypomagnesemia and hypocalcemia: mean total serum Ca concentration (n = 10) and ionized Ca fraction (n = 6) were 5.3 ± 0.9 mg/dL and 3.20 ± 0.80 mg/dL respectively. Mean serum Mg concentration was 1.4 ± 0.5 mg/dL.

Fig. 2. Cause of seizures classified as structural.

with CCN, although seizures resolved. The overall incidence of seizures was 2.5% of the total cattle population referred for neurologic problems.

Discussion

In this study, seizures were mainly reported in beef cattle and the cause could be identified and successfully treated in most cases. Diagnosis relied on thorough history-taking as well as physical and neurologic examinations, CBC, serum biochemistry, CSF analysis, and necropsy.

Idiopathic epilepsy has been described rarely in cattle,[10,11] and the majority of seizures are reactive because of metabolic or toxic disorders.[3] In this study, no idiopathic epilepsy cases were identified. All seizures were because of a reactive or structural cause.

Two of the 4 infectious or inflammatory cases were diagnosed as suppurative meningitis and meningoencephalitis (M-ME), which can arise as a consequence of hematogenous spread of bacteria to the CNS. Failure of passive transfer of colostral immunity can predispose newborn calves to this condition.[12] The most frequently identified etiological agent is *E. coli*, followed by *Streptococcus* spp., *Pasteurella* spp., and *Mycoplasma bovis*.[12] Even with appropriate treatment, the prognosis usually is poor, with a mortality rate approaching 100%.[12–14] In this study, the 2 cases of M-ME, in 1 of which *E. coli* was isolated, were diagnosed in calves and had a fatal outcome.

Bacterial infections involving the forebrain are uncommon in mature cattle. Often manifesting as brain abscesses, they can be caused by extension by a local suppurative process in contiguous areas (eg, sinusitis, otitis, osteomyelitis) or result from hematogenous spread of bacteria. In this study, only 1 animal was diagnosed with a brain abscess resulting from previous trauma to the horn that progressed to frontal sinusitis, as described in the literature.[15]

In the 1 case of Aujeszky's disease (ie, pseudorabies), the presumptive diagnosis was based on self-inflicted skin lesions and a history of contact with swine. The diagnosis was confirmed by the neuropathologic findings at necropsy.

One animal had seizures and died from Pb intoxication. Lead poisoning in cattle usually occurs by ingestion of feed or foreign materials contaminated with exhausted batteries, accumulator batteries, or machine oil. Other sources include lead-based paints, linoleum, or industrial pollution of grazing land.[3,16] That this animal was the only one on the farm to show clinical signs of Pb intoxication may be explained by the fact that it was the only one exposed to Pb. Another possible reason is that, after ingestion, Pb accumulates primarily in the bones but also in the liver and kidneys. When the body is stressed by conditions such as nutritional deficits or pregnancy, Pb is released from these organs into the blood. The ensuing acute increase in serum Pb concentration can cause the clinical manifestations of chronic intoxication.[17] It would have been interesting to measure serum Pb concentrations in the other animals on the farm, but this was not done at the time.

Cerebrocortical necrosis responsive to thiamine was identified as the cause of seizures in 8 animals. Although CCN would fall under the reactive or metabolic classification, in the present study it is classified as secondary or structural because clinical signs occur as a result of structural damage (necrosis) of the cerebral cortex. Although reported to have several different etiologies, the disease is ascribed to a thiamine deficiency or excessive dietary intake of sulfur in most cases.[3,18–20] Indeed, the positive response all affected animals showed to thiamine supplementation substantiates this hypothesis. In the body, thiamine is transformed into thiamine pyrophosphate (TPP) that works as a co-enzyme of several enzymatic systems including erythrocyte transketolase, which is involved in the pentose phosphate pathway and the Krebs cycle. One test for determining thiamine deficiency is the measurement of erythrocyte transketolase activity.[8,19] In field settings, however, the final diagnosis usually is made by examination of the brain at necropsy or after a positive response to treatment with thiamine for practical and economic reasons.

In this study, most cases of reactive seizures were because of electrolyte imbalances in Ca^{2+} and Mg^{2+}. Both minerals are necessary for efficient functioning of the neuromuscular system. Calcium is essential for the transmission of nervous impulses as well as cardiac and skeletal muscle contraction. Its deficiency causes hyperexcitability of the CNS, manifesting as tremor or tetany. Calcium homeostasis is closely related to normal concentrations of Mg^{2+}. Magnesium is an essential cofactor for enzymatic reactions induced by parathyroid hormone (PTH) in bones, kidneys and intestine and for the secretion of the hormone itself.[18] Magnesium modulates parathyroid hormone secretion and upregulates parathyroid receptor expression at moderately low Ca^{2+} concentrations. The body responds to serum Ca^{2+} concentrations below the reference range with the secretion of PTH by the parathyroid glands, mobilizing Ca^{2+} from the bones, increasing its absorption in the intestines, and stimulating the production of vitamin D by the kidneys. The major initial effect when serum Mg^{2+} concentration decreases to <1.6 mg/dL is an altered cellular response to PTH, but when concentrations further decrease to <1.2 mg/dL, the secretion of PTH is completely inhibited.[18]

This mechanism may explain why hypomagnesemia can cause hypocalcemia in cattle, even though hypomagnesemia need not be accompanied by hypocalcemia in some cases.[18,21,22] In our study, hypomagnesemia was an uncommon finding, whereas many cases of hypocalcemia not associated with Mg^{2+} deficits have been identified unexpectedly in growing beef calves. Data in the literature about this condition are scant. A presumptive condition of idiopathic hypocalcemia in 5 foals has been described,[23] but because serum Mg^{2+} concentrations were not measured, a correlation between low Mg^{2+} concentrations and hypocalcemia cannot be excluded.

Another important consideration is that serum Mg^{2+} concentration can increase after intense muscular activity because mechanical damage to muscular tissue leads to direct leakage of Mg^{2+} from the muscle cells into the blood.[24] Because Mg^{2+} concentration in the CSF is not influenced by seizures, its measurement provides a more reliable index of the actual Mg^{2+} concentration in animals presenting with seizures.[24]

The hypocalcemia in these animals could have been caused by nutritional imbalance. This hypothesis is strengthened by the fact that 7 farms referred ≥2 animals with the same diagnosis at the same time. Of note is that all of the animals in which hypocalcemia was identified were Piedmontese calves. A genetic predisposition to the development of this nutritional problem cannot be excluded. Further studies on the Piedmontese breed therefore are needed to investigate this and understand potential genetic factors predisposing to the development of this metabolic defect.

In conclusion, this retrospective study shows that most cases of seizures in our population of cattle are caused by metabolic disorders and that they can be readily managed, with complete remission of seizures. Some permanent visual deficits remained in a few animals with CCN, but the visual deficits did not preclude the possibility of breeding these calves.

Footnotes

Acknowledgments

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