Thiamine-Related Polioencephalomalacia in a Goat

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Introduction

Neurologic diseases can be frustrating for veterinarians to diagnose because numerous etiologies present with similar clinical signs and limited diagnostics are available. Based on thorough history and physical examination, a veterinarian may propose a list of diseases that are most likely and treat accordingly. In food animals, it is imperative to consider that many cases of neurological disease may more commonly occur secondary to other systemic disease or a change in management practice rather than to primary neurological disease. However, primary neurological diseases should not be discounted.

History and Presentation

Ace, an approximately 4-year-old Nigerian wether, presented to Mississippi State University-Animal Health Center, Food Animal department on February 9, 2018, at 9:18 AM for acute onset of seizures, blindness, and ataxia. Behavioral abnormalities were first noted approximately two hours prior to presentation as depression, ataxia in the hindlimbs, extended neck, and opisthotonos. The first seizure occurred en route to the hospital. No medications were administered prior to presentation. Regarding environment, Ace shared seven acres with pregnant does where he had access to a barn for shelter, pasture for grazing, and fresh water ad lib; no other animals were noted to be affected at this time. Regarding diet, Ace was fed a medicated, balanced grain diet for goats (Noble Goat) and occasionally beet pulp with sweet feed. A mineral block was added to Ace's pen a few days prior to presentation. Prior to recognition of neurologic signs, Ace was noted to have a normal appetite and mentation. His vaccination and deworming status were unknown. In May 2014, Ace presented for a one-day history of obstructive urolithiasis which was treated with urethral process amputation, ammonium chloride, ceftiofur, and meloxicam; recovery was uncomplicated.

On presentation, Ace was depressed and exhibiting opisthotonos. A second seizure, which lasted approximately 15 seconds, occurred shortly after arriving at the hospital. During this seizure, vocalization occurred, and his legs and neck were fully extended and rigid. Rescue diazepam (10 mg) and thiamine (1 g) were administered intravenously immediately. Once the seizure subsided, a full physical examination was performed. Ace was normothermic (temperature: 102.8 °F), mildly tachycardiac (pulse rate: 120 beats per minute), and severely tachypneic (respiratory rate: 140 breaths per minute). Ace weighed 45.4 kgs (100 lbs) and was assigned a body condition score of 7/9. His mucous membranes were pink and moist, and the capillary refill time was less than two seconds. Normal bronchovesicular sounds were auscultated bilaterally; no arrhythmias or murmurs were noted on cardiac auscultation. No rumen contractions were auscultated. On examination of the head and face, the following abnormalities were noted: slight head tremor, head tilt to the right, drooping right ear, absent pupillary light reflex and menace response bilaterally, no response to noxious stimuli (pinching of the skin) around the nostrils and lips, and the tongue was easily exteriorized and lacked tone. Bruxism was noted. The remainder of the physical exam was unremarkable. Based on history and physical examination, central neurologic disease due to polioencephalomalacia or bacterial meningitis, such as *Listeria monocytogenes*, were the primary differential diagnoses.

Pathophysiology

Polioencephalomalacia (PEM), commonly known as "polio" for short, is a disease condition that is named based on the histologic lesion that may arise from various etiologies. Literally meaning softening or necrosis of regions of the gray matter in the brain, PEM may result from alterations in thiamine production or metabolism, excessive sulfur consumption, lead intoxication, or salt poisoning (water deprivation). Of these causes, alternations in thiamine

metabolism and excessive sulfur consumption are most commonly reported when a cause can be identified.[1] However, PEM of undetermined etiology is the most frequently diagnosed cause of seizures in goats and sheep.[2]

Clinical signs of PEM may manifest both subacutely and acutely. In the early stages of the subacute form, the animal will seclude itself from the herd, become anorexic, and ataxic. As the condition progresses, symmetric neurologic signs develop including bilateral cortical blindness, slightly hypermetric gait, head pressing, opisthotonos ("stargazing"), bilateral dorsomedial strabismus, and repetitive chewing. Affected animals are typically afebrile unless they develop muscle fasciculations. In the acute presentation, animals are found laterally recumbent and comatose, and they may experience episodic tonic-clonic seizures. In general, the prognosis is poor for acutely affected animals and animals displaying advanced clinical signs of subacute form.[1,3,4]

At the molecular level, PEM is hypothesized to result from energy, adenosine triphosphate (ATP), depletion causing a malfunction of the sodium-potassium ATP-ase pump which allows water to accumulate inside neuronal cells with sodium and results in cellular swelling. The calvarium limits the expansion of neuronal cells causing pressure necrosis of the neuronal tissue as it is pressed against the bony calvarium.

The brain is solely dependent on aerobic metabolism for energy production. A deficiency of enzymatic cofactors responsible for executing aerobic metabolism can inhibit ATP synthesis. Thiamine (Vitamin B_1, aneurin) compounds play a role in many glycolytic pathways. Thiamine pyrophosphate is a necessary coenzyme for α-ketoglutarate dehydrogenase, which functions in the Kreb's cycle to create nicotinamide adenine dinucleotide (NADH). NADH then enters the

electron transport chain to produce ATP. Therefore, a thiamine deficiency either relative or absolute could significantly interfere with ATP production in the brain.[1,4]

It is of considerable importance to appreciate that ruminants rely solely on thiamine production by ruminal microflora to meet their daily thiamine requirements, unlike monogastric animals which ingest their daily thiamine requirements. Therefore, any disturbance in the ruminal microflora predisposes a ruminant to developing PEM. Possible mechanisms which may affect production, absorption, or function of microbial thiamine include production of microbial thiaminases, ingestion of plant thiaminases, or ingestion of inactive thiamine analogs. Thiaminases are enzymes that function to cleave active thiamine to render it permanently inactive. Two types of thiaminases are described, thiaminase I and thiaminase II, and are distinguished by where they cleave thiamine. A few species of *Bacillus* and *Clostridium sporogenes* produce thiaminases; their proliferation is favored with high grain diets. Plant thiaminases function similarly to bacterial thiaminases; plants which contain thiaminases and are native to North America include bracken fern (*Pteridium aquilinum*) and horsetail (*Equisetum arvense*). Nardoo (*Marsilea drummondii*) is native to Australia and contains up to one hundred times the amount of thiaminase activity compared to bracken fern.[4,5] Amprolium is the most commonly reported cause of PEM due to ingestion of an inactive thiamine analog.[1]

Although more commonly reported in beef cattle, sulfur-related PEM must also be considered in small ruminants. In cases where sulfur-related PEM is suspected, food and water sources should be analyzed. Feed additives such as gypsum and ammonium sulfate, feedstuffs such as corn-processing by-products, cruciferous crops, molasses, and fertilizers are potential sources of sulfur. Water may also be a source of sulfur in the form of sulfate.[1,4] It is important to consider that the effects of sulfur are additive.[3] When sulfur is ingested, it is ultimately

converted into sulfide by ruminal microflora. Sulfide is highly cytotoxic and normally undergoes hepatic oxidation to sulfate. When the amount of sulfide overwhelms the capacity of hepatic detoxification, sulfide is hypothesized to inhibit cytochrome-c oxidase, which is a required enzyme in the electron transport chain, and thereby interrupts ATP synthesis.[1,4]

Other causes of PEM, not related to thiamine or sulfur, are briefly discussed. Lead toxicosis acts similarly to sulfide and impairs ATP synthesis causing PEM. Salt poisoning (water deprivation) does not interfere with energy production but instead causes neuronal edema by an osmotic gradient in which extracellular fluid shifts rapidly inside of cells.[1,4]

Along with PEM, bacterial meningoencephalitis must be considered as a potential cause of central neurologic disease. Listeriosis, also known as circling disease or silage disease, is an acute infection with *Listeria monocytogenes*. Clinical forms of the disease include septicemia, abortion, ocular manifestations, and neurologic disease. The nervous manifestation is characterized by asymmetric signs reflecting dysfunction of the brainstem, most commonly the pons and trapezoid bodies; there are usually conscious proprioceptive defects, head pressing, and cranial nerve deficits with cranial nerves V through XII most commonly affected. *Listeria* organisms produce a hemolysin, listeriolysin-O toxin that is responsible for its pathogenicity; however, the exact cytotoxic mechanism is still unclear. Possible routes of infection for nervous Listeriosis may be ascending infection through tooth roots or hematogenous spread.[6]

Diagnostic Approach/Considerations

The presumptive diagnosis of polioencephalomalacia is usually made based on a thorough history and physical examination. Furthermore, a diagnosis of thiamine-related PEM is made based on response to aggressive therapy with parenteral thiamine. Although basic hematology and serum biochemical analysis may be easily performed, the results are usually not

remarkable and, therefore, do not aid in the definitive diagnosis. Thiamine deficiency is difficult to establish and may not be present in many cases, especially those with sulfur-related PEM. Additionally, laboratory tests for thiamine or other enzymes involved in thiamine synthesis in blood or tissue are not widely available in a clinical setting. If sulfur-related PEM is suspected, feed and water sources may be tested for sulfur content. Additionally, measurement of hydrogen sulfide content in the rumen gas cap in asymptomatic herdmates may be of diagnostic value.[4]

In any case of PEM, postmortem findings offer a definitive diagnosis. On gross examination of the brain, the cerebral gyri are widened and flattened with some yellowish discoloration and edema. If the brain swelling is severe, the occipital lobes may herniate under the tentorium cerebelli, and the cerebellum may herniate through the foramen magnum. Additionally, necrotic neuronal tissue will autofluoresce when illuminated with ultraviolet light. On microscopic examination of the tissue, there is edema, cortical laminar necrosis, and evidence of phagocytic cells.[1,3,4] Although this method of diagnosis may not be preferable in the case of an individual companion animal, it may be of considerable diagnostic value in cases of herd health.

Regarding listeriosis, thorough history and physical examination are again the cornerstone of presumptive diagnosis. Analysis of the cerebrospinal fluid (CSF) may be beneficial to support the diagnosis with inflammatory cells and protein seen on cytology. However, increasing cell and protein concentrations are not correlated to the severity of the disease. *Listeria monocytogenes* is only rarely cultured from CSF. Like PEM, listeriosis is definitively diagnosed on postmortem lesions, multifocal microabscessation of the brainstem and identification of *Listeria monocytogenes* from infected tissue. Macroscopic lesions include congestion of the meninges and clouding of the CSF. On microscopic examination of the affected tissue, perivascular cuffing of mononuclear cells is characteristic along with multifocal,

asymmetric, microabscessation of the brainstem with neutrophils being the predominant cell population.[6]

Treatment and Management

Considering the primary differential diagnoses which can only be definitively diagnosed on postmortem examination, a treatment plan should be formulated to cover both possibilities.

For treatment of polioencephalomalacia, parenteral thiamine supplementation and supportive care is indicated. Thiamine hydrochloride is administered at 10-20 mg/kg intramuscularly or subcutaneously every 6-8 hours. If clinical signs are severe, intravenous administration of the first dose may be warranted. Thiamine should be supplemented for at least 3-5 days past the resolution of clinical signs. Regarding supportive care, diazepam may be administered if the animal is seizing.[1,3,7] Ancillary agents, such as nonsteroidal anti-inflammatory drugs, dexamethasone, DMSO, furosemide, and mannitol, have been used historically to decrease the inflammation and cerebral edema associated with PEM, but at this time there are no clinical studies assessing their effectiveness for treating these conditions in ruminants.[2,7] Although most affected animals respond favorably to therapy, it is possible for them to retain some permanent visual impairment or neurologic deficit, and they may be ultimately culled or euthanized due to poor performance.[1]

For treatment of listeriosis, *L. monocytogenes* is susceptible to most commonly used antimicrobials with oxytetracycline or penicillin G being recommended. Oxytetracycline is typically administered at 10 mg/kg intravenously every 12 hours, while penicillin is administered at an initial dose of 40,000 IU/kg intravenously (potassium penicillin G) every 6-8 hours for 7 days and then 22,000 IU/kg intramuscularly (procaine penicillin) every 24 hours for 14-21

additional days. The prognosis is best for animals if they are treated early. Despite intensive antibiotic therapy, recumbent or convulsive animals rarely survive.[6]

Case Outcome

After initial stabilization with intravenous diazepam and thiamine, a blood sample was collected to measure sodium levels to exclude salt toxicosis (water deprivation) as a cause of polioencephalomalacia. Sodium levels were within normal limits (sodium: 147.7 mmol/mL, reference range: 141-156). Oxytetracycline (900 mg) was administered intravenously, along with dexamethasone (4 mg). Ace was hospitalized on February 9th for monitoring. Over the next six hours, Ace's mentation improved; he became bright, alert, and responsive. Because of his acute blindness, he remained stationary in his stall initially but slowly began to explore his surroundings as he became more comfortable. By 4 PM, a delayed menace response, normal palpebral reflex, and normal pupillary light reflex were present bilaterally, and he responded to noxious stimuli (pinching) around his nose and lips, and he had normal tongue tone. Ace still retained some degree of visual impairment because he would occasionally be seen bumping into the stall walls or stumbling over his feed pans. No other episodes of seizures or seizure-like activity were noted throughout the day or overnight. Due to his rapid improvement with treatment, Ace was presumptively diagnosed with thiamine-related PEM. Ace was hospitalized for a total of five days. Regarding treatment, thiamine (500 mg) was administered every six hours from February 9th through February 13th, dexamethasone (4 mg) was administered intramuscularly on February 10th, and oxytetracycline (900 mg) was administered subcutaneously on February 10th and 12th. His visual acuity continued to improve slowly; he became able to distinguish shadows and movement. On February 12th, Ace became anorexic

with decreased ruminal contractions; a rumen transfaunation was performed once daily for the next two days. His appetite improved.

Ace was discharged on February 13, 2018, with instructions for the owner to continue to monitor Ace and the rest of her herd for any changes in behavior or neurologic signs. If abnormalities were seen, she should administer a subcutaneous injection of thiamine (500 mg/100 lbs) immediately and seek veterinary care as the animal may be experiencing an episode of PEM. Additionally, we recommended housing Ace with other friendly goats to serve as his companions to help him navigate his surroundings; the pasture should not have any dangerous obstacles as Ace may have permanent visual deficits.

Ace's owner was contacted two weeks after discharge; she reported that Ace was doing well at home. The first three days that Ace was home she was able to appreciate that he still had visual deficits seeing primarily shadows and movement. However, she believed that his vision had improved with time. She commented that his appetite was slightly decreased the first three days at home but had since returned to normal. When questioned about the herd, she commented that none of Ace's herd mates exhibited any signs of lethargy, anorexia, mental dullness, or neurologic signs since Ace was presumptively diagnosed with polioencephalomalacia.

It is important to note that Ace's outcome is not typical as most cases of PEM may survive the initial insult but are euthanized secondary to residual deficits that prevent the animals from thriving as productive members of the herd. It is likely that the owner's vigilance and swift action to seek veterinary care contributed to Ace's favorable outcome. While polioencephalomalacia may occur secondary to numerous etiologies, the cause of PEM in this case was undetermined.

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