A Neurologic Myster-iosis

A Case Report of Caprine Encephalitic Listeriosis

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Introduction

Listeriosis is an infection caused by the organism *Listeria monocytogenes* and produces an acute meningoencephalitis found in a wide range of mammals, including ruminants, monogastric animals, and humans; as well as in fowl.[1,4] Encephalitic listeriosis, the most common form of the disease in ruminants, is often sporadic, with two of the most common risk factors being the feeding of poorly preserved silage and crowded winter housing.[1,6] Although unilateral cranial nerve deficits are the hallmark of the disease, it may manifest as a multifocal brainstem disorder with multiple cranial nerve deficits, diffuse meningoencephalitis, or myelitis.[1,6] A presumptive diagnosis is usually based on clinical and neurological signs, but listeriosis can only be definitively diagnosed at necropsy.[1] The earlier in the course of disease that treatment is administered, the higher the chances of recovery; however, once recumbency has occurred in ruminants, prognosis is poor.[1,6] The case fatality rate in ruminants left untreated approaches 100%.[1,8]

History and Presentation

Little Buddy, an approximately 1.5-year-old Nigerian Dwarf-cross wether, presented to the Mississippi State University College of Veterinary Medicine Food Animal Department on November 3, 2018 with a one-week history of lethargy and progressive neurological signs consisting of ataxia, circling, and head-pressing over the three days prior to presentation. He was observed eating peanuts, leaves, wild pears, and sweet feed the week prior to becoming ill but had reportedly only eaten hay and leaves since. Little Buddy was last seen standing the afternoon before presentation. He had a history of ingesting motor oil in February 2018 for which he was treated at MSU-CVM and recovered uneventfully.

Upon presentation, Little Buddy was dull, depressed, and recumbent. Little Buddy weighed 46.3 kg and was tachycardic with a heart rate of 116 beats per minute (normal: 70-80 beats per minute), tachypneic with a respiratory rate of 40 breaths per minute (normal: 12-24 breaths per minute), and pyrexic with a rectal temperature of 106.5 ºF (normal: 101.5-103.5 ºF). His mucous membranes were pink and moist with a capillary refill time of less than 2 seconds. An inspiratory stertor was auscultated in the trachea. Little Buddy's abdomen appeared slightly distended and ruminations were quiet but otherwise normal at 2 per 2 minutes.

Upon neurological examination, there was an absent menace response and palpebral reflex of the right eye as well as medial strabismus of the left eye. A head tilt to the left was present and at one point during the examination, Little Buddy stood and circled tightly to the left. Moderate ptyalism was observed, especially from the right side of the mouth, and his tongue appeared paralyzed on the left side, as it protruded outward on that side only. Based on the history and clinical evidence of multiple cranial nerve deficits, Little Buddy was given a presumptive diagnosis of encephalitic listeriosis.

Pathophysiology of Disease

Encephalitic listeriosis, also known as "circling disease" or "silage disease," is an acute meningoencephalitis associated with *Listeria monocytogenes,* a Gram positive, intracellular, facultative anaerobe.[3,4] *L. monocytogenes* is most often shed in feces and is ubiquitous in the environment, but shedding in milk and uterine discharges is also possible.[1] There is a growing concern regarding the zoonotic potential of listeriosis from milk and dairy products of goats because it is possible for the organism to be shed in the milk of both clinically affected individuals and apparently healthy latent carriers.[9] Shedding of *L. monocytogenes* is less likely to occur in the encephalitic form of the disease than in the septicemic or abortive forms, as the

organism is usually confined to the brain.[1,9] Direct transmission of *L. monocytogenes* from animals to humans is uncommon.[9] The organism can survive for up to two years in the environment and has been found to be resistant to freezing and thawing in the soil.[4] The prolonged survival of *L. monocytogenes* in the environment may be due to its ability to readily produce biofilms, which can persist on processing or farm equipment that is not properly cleaned and aid in the perpetuation of the organism on infected farms.[3,9] Although listeriosis can be found worldwide and can occur at any time of the year, it tends to occur most frequently in temperate climates during the winter months.[4,6] Consumption of improperly fermented or contaminated silage and rotting vegetation are common sources of infection, but goats that consume woody browse may have an increased risk of contracting the disease.[3,8] The disease has also been found in animals consuming pasture, hay, and soybean products.[1] It is possible that the source of bacteria in a patient may not be discovered. Bacteremia, septicemia, or placental and fetal infection in ruminants may occur due to *L. monocytogenes* penetrating mucosal surfaces, especially through abrasions in the oral cavity caused by hard feed material or during periods of tooth loss or eruption.[1,8]

The pathogenesis of encephalitic listeriosis is an ongoing debate. Hematogenous spread of *L. monocytogenes* and ascending infection via the rootlets of various cranial nerves are the two most common theories as to how infection of the brain occurs.[1,6] There is strong evidence of intra-axonal migration of the organism into the brainstem in otherwise healthy humans and ruminants that contract rhombencephalitis (brainstem encephalitis).[5] It is believed that *L. monocytogenes* can spread further along axonal connections between the brainstem and higher centers upon gaining access to the central nervous system via axons of the peripheral nervous system.[7] The reason that *L. monocytogenes* is able to survive phagocytosis and spread

intracellularly is that once the organism is enclosed in a phagolysosome, the low pH induces an exotoxin called listeriolysin-O to lyse the phagolysosome membrane and allow *L. monocytogenes* access to the cytoplasm.[6] In the cytoplasm, the organism proliferates and forms elongated outpouchings called filopods that are ingested by neighboring cells.[6] This process allows cell-to-cell movement of the organism with no extracellular contact.[6]

The onset of encephalitic listeriosis is usually acute and the disease often progresses rapidly.[5] Early signs may be non-specific and include: depression, anorexia, and possibly a fever of up to 107.6 ºF.[9] Encephalitic listeriosis may manifest as a multifocal brainstem disorder with multiple cranial nerve deficits, diffuse meningoencephalitis, or myelitis.[1] However, unilateral cranial nerve deficits are the hallmark of the disease, with affected animals showing potential dysfunction of cranial nerves V through XII.[1,4,6] A dysfunctional trigeminal nerve (CN V) causes a loss of facial sensation, with a poor jaw tone, inability to eat, and facial analgesia or anesthesia being common findings.[1,6] Animals with loss of function of the abducens nerve (CN VI) exhibit a medial strabismus on the side ipsilateral to the lesion because the lateral rectus muscle is affected.[1] Deficits of the facial nerve (CN VII) result in an ipsilateral ear droop, ptosis, and a drooped lip.[1,6] Ipsilateral losses of the menace response, palpebral reflex, and levator nasolabialis muscle function can be seen with decreased motor function of the facial nerve, and the nasal philtrum is often deviated to the side opposite of the lesion in small ruminants and camelids with CN VII loss.[1,6] Lesions of the vestibulocochlear nerve (CN VIII) manifest as an inconsistent and variable (mainly horizontal or vertical) nystagmus that may change with altered position of the head.[1] A head tilt with circling, leaning, or falling toward the side of the lesion is common with CN VIII involvement.[1,6] If the cerebellar peduncles are involved, these clinical signs may manifest toward the side contralateral to the lesion – a rare incidence called paradoxical

vestibular syndrome.[1,6] A lesion of the vagal nerve (CN X) can cause stertorous breathing, while dysfunction of the hypoglossal nerve (CN XII) can cause paresis or paralysis of the tongue, causing it to protrude from the side of the mouth ipsilateral to the lesion.[1,4] Dysfunction of the glossopharyngeal nerve (CN IX), vagal nerve, and hypoglossal nerve result in dysphagia, which can cause anorexia, dehydration, ptyalism, and accumulation of feed material in the oral cavity.[1,4,6] Conscious proprioceptive deficits, which are caused by interference with the descending motor pathways and the ascending proprioceptive fibers in the brainstem, as well as head pressing, caused by lesions in the basal ganglia, may also be present.[4]

Diagnostic Approach and Considerations

A presumptive diagnosis of encephalitic listeriosis is often based on a patient's history, e.g. consumption of silage or rotten vegetation, and classic neurological signs of multifocal or unilateral cranial nerve deficits.[1] Although there are few useful antemortem diagnostic tests, cytologic analysis of the cerebrospinal fluid may be used to support a presumptive diagnosis.[1] Characteristic findings include increased total protein concentration (>40 mg/dl) and nucleated cell count (>12 cells/μl), with mononuclear cells predominating.[1] The results of CSF analysis do not seem to correlate with the severity or outcome of disease.[1,6] Culturing the CSF is often unrewarding because it is extremely difficult to isolate *L. monocytogenes* despite the use of enrichment methods.[6] However, the organism is recovered best from refrigerated nervous tissues, and enrichment may be accomplished via refrigeration of brain slices at 4ºC for 3 months, with weekly subculturing of the tissues.[1]

Other diagnostics utilized in the presumptive diagnosis of listeriosis may include a complete blood count and serum biochemistry profile, but these are not crucial in the diagnosis of the disease.[1] Although parameters are often within normal limits, abnormalities usually reflect

stress via a mature neutrophilia and lymphopenia, dehydration, and the acid-base status of the patient.[1,6] Listeriosis is one of the few conditions of adult ruminants in which metabolic acidosis is frequently observed, but it is not diagnostic for the disease and simply reflects an excessive loss of saliva.[6] Advanced imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) may be explored, but the resolution of CT scans has proven inadequate to gain insight into the neuropathology of rhombencephalitis, and MRI has been shown to allow visualization of diffuse but so far fairly unspecific lesions.[2]

A definitive diagnosis of encephalitic listeriosis can only be confirmed at necropsy and requires histologic examination of tissues due to a lack of gross lesions.[2,6,8] Characteristic histopathologic lesions include microabscesses that consist of asymmetrical, multifocal to coalescing areas of necrosis in the brainstem; marked perivascular cuffing with mononuclear cells; and meningoencephalitis.[1] As mentioned previously, culture of *L. monocytogenes* is difficult but possible; however, no media or cultural techniques promoting the isolation of the organism have been found to successfully confirm the diagnosis of listeriosis.[1,6] Therefore, observation of the histopathologic lesions is often considered diagnostic for encephalitic listeriosis even if the organism is not isolated.[1,6]

It is important to note that there are several other neurologic conditions which may produce signs similar in appearance to listeriosis and should be considered when diagnosing a ruminant with neurologic disease. These differential diagnoses include rabies, polioencephalomalacia, cerebrospinal nematodiasis or aberrant parasite migration, brainstem abscess or neoplasia, otitis media/interna, pituitary abscess syndrome, the neurologic form of caprine arthritis encephalitis virus, or head trauma.[1,6,9] A thorough physical and neurological

examination, as well as a cerebrospinal fluid analysis, are generally adequate to distinguish listeriosis from other differentials.[6]

Treatment and Management

The course of disease of encephalitic listeriosis is much shorter in small ruminants than in cattle, usually lasting one to four days in goats with death potentially occurring in as little as two to four days after clinical signs first appear.[1,9] In cattle, death may not occur until about two weeks after the appearance of initial clinical signs.[1] The chances of survival are greatest the earlier that treatment is instituted.[1] As the severity of the disease progresses, animals become recumbent, unable to rise, and may lie on the same side as the lesion.[1] Torticollis, opisthotonos, and convulsions may occur in severely affected animals.[1,8] Once recumbency or paralysis has developed, the prognosis significantly worsens, and treatment is usually unsuccessful.[6] High case fatality rates can occur even with prompt treatment, especially in sheep and goats.[6] In untreated ruminants, case fatality rate is nearly 100%.[1,8]

Antibiotic therapy is the preferred treatment for encephalitic listeriosis, with the most effective drugs being those which penetrate the intracellular space, cross the blood-brain barrier, and are bactericidal.[1] The most commonly employed antimicrobials for the treatment of encephalitic listeriosis in ruminants are penicillin (22,000 to 44,000 IU/kg, IV, Q6; or IM, Q12) and oxytetracycline (20 mg/kg, IV, Q24; or 10 mg/kg, IV, Q12).[6] Successes and failures have been reported with both drugs, and controlled clinical trials comparing these antimicrobials *in vivo* against *L. monocytogenes* have not been explored.[6] An extended course of antibiotic therapy lasting two to four weeks is recommended to ensure complete resolution of disease and prevention of relapses.[1,6] Other adjunct therapies include supportive nonsteroidal or steroidal anti-inflammatory drugs, fluids, electrolytes, rumen transfaunation, B vitamins, and feed

mashes.[6] The use of dexamethasone is controversial due to its inhibiting effects on the cell-mediated immune responses, but it can be helpful to treat inflammation of the brain.[3,6]

After a complete physical and neurological examination, Little Buddy received florfenicol (40 mg/kg, SC, once), thiamine HCl (10 mg/kg, SC, Q6), oxytetracycline (20 mg/kg, IV, Q24), dexamethasone (0.1 mg/kg, IV, Q48), and flunixin meglumine (1.1 mg/kg, IV, once). Multiple cranial nerve deficits remained the following day with minor improvement. An orogastric tube was placed into the rumen on day 3 of hospitalization and a Na-K-Cl solution was administered. A serum chemistry panel was performed, revealing a significant hypokalemia (2.09 mmol/L, reference: 3.40-6.80 mmol/L), moderate metabolic acidosis (TCO_2 19.5, reference: 25.0-31.0), moderate hyperglycemia (230 mg/dl, reference: 49-76 mg/dl), moderate azotemia (BUN 70 mg/dl, reference: 9-21 mg/dl; Creatinine 3.34 mg/dl, reference: 0.90-1.90 mg/dl), and a significantly elevated AST (635 U/L, reference: 45-162 U/L) and CK (40220 U/L, reference: 103-220 U/L). Little Buddy was started on an intravenous Lactated Ringers Solution at a double maintenance rate of 60 ml/kg/day with 20 mEq KCl / 1 L LRS added.

Little Buddy was administered an intravenous Vitamin B complex solution at a rate of 5 ml / 1 L LRS on day 4. He also received 800 IU of a Selenium-Vitamin E injection subcutaneously. Little Buddy was observed having six seizure-like events in the span of 15 minutes in his stall on day 5. However, he never appeared to lose consciousness, so these events may be more consistent with vestibular episodes. Little Buddy received an intravenous administration of 25% mannitol solution (1 g/kg). Glucostix and ketostix tests were performed, revealing a moderate hyperglycemia of 196 mg/dl (normal: 45-70 mg/dl) and a normal ketone value of 0.1 mmol/L.

Upon evaluation by the MSU-CVM Neurology service on day 6, Little Buddy's lesion now showed diffuse brainstem involvement with potential cerebellar involvement based on development of hypermetria of the forelimbs, and he was found to have decreased ear movement on the right side, trochlear nerve dysfunction, trigeminal nerve dysfunction, and facial nerve dysfunction. A CBC and repeat serum chemistry panel were performed, with the CBC showing no abnormalities, and the serum chemistry panel revealing a mild hyperglycemia (117 mg/dl), moderately elevated AST (355 U/L), and mildly elevated CK (1250 U/L). Little Buddy received another dose of dexamethasone (0.1 mg/kg, IV), and was started on ivermectin (200 μl/kg, SC, Q24, for 5 days), fenbendazole (50 mg/kg, PO, Q24, for 5 days), and procaine penicillin G (44,000 IU/kg, SC, Q24). Due to the atypical waxing and waning of Little Buddy's clinical signs, he was treated concurrently for several other neurologic differentials (polioencephalomalacia, neurologic parasitism, and bacterial/viral meningoencephalitis), as a definitive diagnosis of encephalitic listeriosis can only be made postmortem. A cerebrospinal fluid analysis and MRI were also pursued. The CSF analysis revealed the following values: nucleated cells 280 /μl (normal: <20 nucleated cells /μl); protein 53.0 mg/dl (normal: <15 mg/dl). There was a marked lymphocytic pleocytosis upon cytologic examination, with a predominance of small lymphocytes and some large mononuclear cells. At the Veterinary Specialty Center, Little Buddy was premedicated with 0.05 mg/kg xylazine and 0.025 mg/kg butorphanol, then induced with 5 mg/kg ketamine. He was intubated with a 7.0 mm endotracheal tube and maintained under general anesthesia on isoflurane for the duration of the MRI. Little Buddy recovered from anesthesia uneventfully with only minor regurgitation. The MRI revealed multiple variably sized, patchy, intramedullary, heterogeneously contrast-enhancing, T2 and T2 FLAIR hyperintense, T1 isointense regions within the brainstem (mesencephalon and metencephalon),

suggestive of infectious etiologies such as neurolisteriosis (rhombencephalitis), with metabolic, nutritional, or toxic etiologies considered less likely.

Case Outcome

Little Buddy's neurologic status continued to improve daily after day 10 of hospitalization. The head-pressing gradually ceased, the circling lessened day by day, and he was able to walk in a relatively straight line by day 14. Other cranial nerve deficits appeared to improve over time as well. A neurological examination was performed on day 16, revealing significant improvement in neurologic status with only minor deficits in cranial nerves VII (weak palpebral reflex and delayed menace response of the right eye; decreased sensation to the right nares) and VIII (minor head tilt to the left). Little Buddy was discharged on day 16 and remained on procaine penicillin G (44,000 IU/kg, SC, Q24) until he returned to MSU-CVM two weeks later, when another neurological examination was performed. At this time, he was found to have mildly delayed palpebral and menace responses on the right side but was able to ambulate and navigate with no issues. As of June 2019, Little Buddy's owner says he is doing extremely well at home and his only noticeable remaining deficit is a very slight head tilt.

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