Locked in: A puppy's fight against a cruel Clostridial

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Introduction

Tetanus is a toxigenic illness caused by the anaerobic, spore-forming, gram positive bacteria, *Clostridium tetani.*[1] The most severe clinical signs are seen with the generalized form of tetanus. Clinical signs include extreme muscle rigidity and very commonly signs of cranial nerve involvement such as risus sardonicus, trismus, protrusion of the third eyelid, laryngeal spasm and dysphagia.[2] Diagnosis is usually based on clinical signs and prognosis for generalized tetanus is often grave due to the extensive supportive care required.[3] This paper will discuss multiple treatment modalities including several pharmacologic interventions not described in previously reported tetanus cases, as well to showcase the extensive supportive care provided in the successful treatment of a rare case of generalized tetanus in a puppy.

History and Presentation

A 4-month old, male intact, husky who presented to MSU-CVM's Veterinary Specialty Center (VSC) for an acute episode of a stiff wobbly gait, pulled back ears and taut skin around his eyes and mouth. When questioned, the owners mentioned the patient was teething and had been seen chewing on a rusty bolt several days prior to presentation. Neurological examination found normal mentation, stiff, stilted gait, intermittent increased muscle tone diffusely over the entire body, spastic facial paresis with retracted ears, and his tongue was deviated slightly to the left. His cranial nerves, postural reactions and reflexes appeared otherwise normal and no hyperpathia was noted. Due to these clinical signs, a presumptive diagnosis of tetanus was made and the patient was transferred to MSU-CVM's Intensive Care Unit (ICU). Other differentials for these clinical signs include toxicities such as Strychnine, organophosphates, and metalaldehyde as well as, meningoencephalitis, spinal trauma, acute cerebellar disease or drug reactions.[4] Due to the patient's young age, history and clinical signs, tetanus was considered the most likely diagnosis.

Treatment

Once transferred to ICU, lactated Ringer's with 2.5% dextrose (fluid rate of 20ml/hr) were started as well as oral metronidazole (10 mg/kg q12h), intravenous midazolam (0.2 mg/kg q8h) and intravenous dexmedetomidine (3mcg/kg q6h) as needed for sedation/anxiety. The patient was also placed in a quiet, dark area of ICU and soft cotton was placed in both ears to reduce noise.

On day 2, the patient had become more agitated, had increased extensor rigidity and intermittent hypersalivation. Due to the rapidity of his declining condition his treatment plan became more intense and included: intravenous metronidazole (10mg/kg q12h), started on unasyn (30 mg/kg IV q8h) to aid in eliminating any remaining Clostridial bacteria present and started on cerenia (1mg/kg q24h IV) to help decrease any hypersalivation due to nausea. An esophagostomy tube (E-tube) and jugular catheter were placed. Correct placement was confirmed on thoracic radiographs. Tetanus antitoxin (Equine origin, 300 IU IM once) was administered to help bind any remaining toxin in the patient's system. A single dose of Benadryl (2 mg/kg IM once) and a single dose of dexamethasone SP (0.1 mg/kg IV once) was given prior to antitoxin administration to minimize any adverse reactions. A midazolam constant rate infusion (CRI) was started (0.5 mg/kg, 0.9 ml/hr) along with a magnesium sulfate CRI (40 mg/ml, 1.5ml/hr) for sedation/anxiety and muscle spasms. An accidental bolus of 60mL of the magnesium sulfate CRI was given over one hour resulting in a serum magnesium concentration of 5.5meq/L. No signs of toxicity were seen and the patient recovered without any residual effects. Nursing care treatments included: provision of soft, well-padded bedding, rotating the patient every few hours, aspirating the E-tube, monitoring the E-tube and jugular catheter sites for signs of infection, provision of nutrition (feeding a slurry of food through the E-tube every four hours), lubricating eyes and passive range of motion exercises on all joints every four hours. Bloodwork to determine the patient's metabolic status was normal with the exception of moderately elevated creatinine kinase (CK) levels.

Over the next several days, the tetany progressed to the fore and hind limbs keeping them rigidly extended and eventually forcing him into an opisthotonus position. The patient had intermittent episodes of vocalizing, increased extensor rigidity, anxiety, increased respiratory rate and increased temperature due to autonomic dysfunction. A dexmedetomidine CRI was started and adjusted as needed to acquire adequate sedation (1- 4.5 mcg/kg/hr). Oral methocarbamol (1 tab – 50mg q8h) was also added to treatments to help with muscle spasms. Midazolam and dexmedetomidine boluses were given as needed for additional sedation. Methadone (0.1mg/kg IV q6h) was added to control pain. Pantoprazole (1 mg/kg IV q24h) was added as a gastroprotectant. Mild hyperglycemia was noted on blood work at this point so dextrose fluids were discontinued and replaced with plasmalyte. On day 6, the patient had an episode of dyspnea after being overstimulated during feeding. His mucous membranes became slightly cyanotic and he was provided with flow by oxygen and improved. TFAST ultrasound was normal though auscultation revealed harsh lung sounds and referred upper airway noise. Radiographs showed small focused areas of mild alveolar pattern suggestive of pneumonia.

On day 7, the patient had a second episode of dyspnea during morning feeding though he quickly recovered with flow by oxygen. Throughout the day and for the next several days, the patient continued to have episodes of hyperthermia, dyspnea, hypersalivation and tachypnea. These episodes were managed with suction for hypersalivation, provision of flow-by oxygen and dexmedetomidine boluses. Ondansetron (0.2 mg/kg IV q8h) was added to help address hypersalivation and nausea. The dexmedetomidine CRI (5.0 mcg/kg/hr) was increased to address his worsening agitation and fluid rate was decreased due to possible pneumonia (10ml/hr). On day 8, mild crackles in the right lung field and a wet sounding cough developed so the patient's fluids were discontinued. The magnesium CRI was increased (40mg/ml, 8ml/hr) because serum magnesium concentration (3.2 mg/dL) was not in the target therapeutic range of 4.63-8.34 mg/dL.[5] On days 9 and 10, a fentanyl CRI (3-5 mcg/kg/hour IV) and gabapentin (1 tab – 10mg PO q12h)

were started to control pain. Large volumes of dark brown hemorrhagic liquid began being aspirated from the E-tube. A metoclopramide CRI (3mg/kg/day, 10ml/hr) was started to help promote gastrointestinal motility and sucralfate (1 tab q8h) was added to help protect and heal esophageal and stomach mucosa. The crackles heard on lung auscultation one-day prior had resolved but lung sounds remained harsh. The magnesium sulfate CRI was again increased (40mg/ml, 10ml/hr) as serum magnesium levels (3.4 mg/dL) were still not within therapeutic range.

The morning of day 11 it was noticed that the patient seemed extremely sedate with accompanying hyperthermia and anisocoria. The dexmedetomidine CRI had been incorrectly mixed resulting in a severe overdose. A malignant hyperthermia resulted. Treatment with atipamazole and intralipid therapy was immediately initiated. The patient recovered but regurgitated twice during the process. After recovering, the dexmedetomidine CRI was slowly reintroduced which was tolerated well. Thoracic radiographs showed evidence of aspiration along with bloodwork which showed an increase in band neutrophils (1110/ul – reference range 0-400).

On day 12, the patient remained unsettled and vocal for most of the day. CBC showed increased white blood cells (29.1 K/ul – reference range 7.0 -22.0) and increased segmented neutrophils (24,444/uL – reference range 3500 – 14200) suggestive of aspiration pneumonia. By day 13 the patient was showing motor function in the back legs and bloodwork showed the segmented neutrophil counts to be back within normal range.

For the next several days, the patient continued to improve and slowly regain further range of motion in all his joints. His sedation and intravenous pain medication was slowly decreased as he improved. By day 18, the patient was able to pull himself into sternal position, occasionally stand and swallow. Oral medications were started including metronidazole (10mg/kg PO q12h), cerenia (2mg/kg PO q24h), clavamox (13.75 mg/kg PO q12h) and omeprazole (7mg cap PO q24h) given in small meatballs of soft puppy food.

The patient continued to improve to the point where he was able to move freely around his kennel so on day 20 his jugular catheter was removed and all CRIs were discontinued. Trazodone (3mg/kg PO q8h) and diazepam (0.5mg/kg) were given to assist in sedation due to anxiety and to continue to provide some muscle relaxation. On day 23, the patient's metabolic energy requirement was re-calculated to be approximately 1,500 kcal/day and he was started on a more aggressive feeding schedule to help regain weight. Over the course of treatment patients body condition score had decreased to a 2-3/9. On day 24 the patient was eating well on his own and having no evidence of residual dysphagia, laryngeal spasm or hypersalivation after more aggressive feedings. The E-tube was removed and all medications were stopped except for the oral medications he was to be sent home on. On day 25 of hospitalization the patient was discharged with the following medications: trazodone (50mg tabs – 3mg/kg) PO as needed, diazepam (5 mg tabs– 0.5mg/kg) PO q8h for 14 days, metronidazole (10 mg/kg PO q12h) for 14 days, clavamox (20 mg/kg PO q12h) for 14 days, omeprazole (7mg capsule PO q24h) for 14 days, methocarbamol (1 tab -50 mg PO q8h) for 14 days and gabapentin (100mg/ml- 1ml PO q12h) for 14 days. The clients were shown how to perform passive range of motion exercises with the patient at least twice a day.

The patient came back two weeks later for a recheck exam. Radiographs revealed complete resolution of the aspiration pneumonia. Owners reported he was doing well at home and the only remaining abnormalities on exam were mildly retracted ears. Several weeks later, the owners reported the patient to be completely back too normal with no noticeable residual effects from his battle with tetanus.

Discussion

Tetanus is a disease caused by the bacterium *Clostridium tetani*. This bacterium forms resistant spores that can survive high temperatures and most common disinfectants. Due to its hardy nature, the spores are ubiquitously found in soil and feces and are able to survive for months to years under optimal conditions. While cats and dogs are 2400 and 200 times respectively more

resistant to clinical tetanus infection compared to humans and horses, they can contract tetanus through a contaminated penetrating wound which often leads to localized infections.[2] Generalized tetanus in dogs has been shown to be associated with tooth eruption, tooth root abscesses, and surgical contamination.[4] Once the bacterium is inoculated into an anaerobic environment, the spores become vegetative and highly pathogenic. Disease usually occurs within 5-10 days after inoculation but this range can extend anywhere from 3-18 days. The vegetative spores produce two toxins, tetanolysin and tetanospasmin. Tetanolysin causes lysing of red blood cells and can cause tissue damage resulting in an optimal local environment for the bacteria to grow.[6,7] Tetanospasmin is the toxin responsible for causing the classical neurological signs of tetanus and attaches to peripheral nerves. Once internalized in the nerve, the toxin is incorporated into a vesicle and is transported retrograde to the central nervous system (CNS) at a rate of 75-250mm/day. The rate of retrograde transport is enhanced by neuronal stimulation.[2,6,8,9] Eventually the toxin reaches the motor nerve dendrites within the spinal cord and the brain stem. Here, the toxin is internalized by inhibitory interneurons and irreversibly binds to presynaptic sites preventing the release of neurotransmitters glycine and gamma-aminobutyric acid (GABA).[2] This causes a general excitability of neurons resulting in generalized muscle spasm and alterations of autonomic control.[2] Recovery requires axon terminals to regenerate which can take 2-3 weeks.[4]

Clinical signs vary depending on whether infection is localized or generalized. Localized tetanus is associated with a lower toxin load and signs of muscle rigidity at the site of infection. Generalized tetanus is more severe and signs can include extreme muscle rigidity with extensor muscle groups dominating throughout the entire body. Signs of cranial nerve involvement are also very common and include the classical signs of tetanus infection: risus sardonicus, trismus, protrusion of the third eyelid, laryngeal spasm and dysphagia.[6,10,11] There may also be signs of autonomic dysfunction including ptyalism, tachycardia, tachypnea and hypertension.[2,10, 12-14] This is caused by a loss of inhibition of autonomic discharge which causes excess sympathetic activity and

excess catecholamine levels. Signs of autonomic dysfunction often begin several days after rigidity and can persist for 1-2 weeks.[2,15,7,16]

Diagnosis of tetanus is often made based on history and clinical signs. Bloodwork is usually non-specific but is helpful as a way to continually assess the patient's status. Diagnosis by means of culturing the organism, toxin identification in the blood and/or gram staining is unsuccessful most of the time and not recommended [4]. Electromyographic changes can be seen in tetanus patients which include prolonged electrical discharges following needle insertion with normal nerve conduction velocities. However, this form of testing if necessary, should be delayed until after treatment as it can result in progression of the disease.[8,12,17]

The main goals of treatment for tetanus are to first neutralize the circulating toxin, debride any wound present, administer antibiotics effective against *C. tetani*, sedatives for muscle spasms, opioids for pain and provide constant monitoring and supportive care. To neutralize the circulating toxin present in the blood, tetanus antitoxin needs to be administered. Tetanus antitoxin products cannot cross the blood brain barrier and can only neutralize toxin in blood and are not effective once toxin enters the nerve cell. It is critical to administer antitoxin as soon as possible to limit the amount of toxin that is able to enter the nerve cells. Recommended dosing is 100-1000U/kg with a max dose of 20,000 U IV, IM or SQ.[6] The amount given should be based on the estimated toxin load and not the size of the patient. There is always a risk of reaction when administering biologic products. Intradermal skin testing has been recommended when giving tetanus antitoxin to decrease the risk of systemic reaction. The patient described in this case was given tetanus antitoxin on the 2nd day of presentation. In an attempt to administer the anti-toxoid quickly, an intradermal test was not performed. Premedication of steroid (dexamethasone SP 0.1 mg/kg IV once) and antihistamine (Benadryl 2-4 mg/kg IM once) were given to decrease the risk of a potential reaction. Fortunately, in this case no adverse reactions were seen.

Proper wound debridement is a critical part of the management of tetanus patients. As it is crucial to remove any necrotic debris that are present creating an anaerobic environment. Antimicrobial therapy is also necessary in order to eliminate vegetative clostridial spores and prevent further toxin release. Metronidazole is the antibiotic treatment of choice because it is bactericidal against anaerobes and rapidly achieves therapeutic concentrations in almost all bodily tissues, including abscess cavities.[18] Suggested dosing is 10mg/kg IV q12h. Penicillin was often used in the past for the treatment of tetanus infections. Metronidazole has become the preferred antibiotic because penicillin like tetanus toxin is a GABA antagonist that can result in increased risk of convulsions[19-21]. Suggested dosing for Penicillin G is 20,000 – 100,000 U/kg IV q 6-12H. Both metronidazole and unasyn were utilized to manage the tetanus infection in this case. Later, clavamox was added to treat aspiration pneumonia that had developed. There are a variety of drugs used to help minimize and control the muscle spasms and rigidity. Most commonly used drugs include phenothiazine, benzodiazepines and methocarbamol.

Benzodiazepines augment GABA agonism at the GABA receptor. Midazolam (0.2-0.5 mg/kg/hr IV CRI) was used in this case versus diazepam due to clinician preference. Dexmedetomidine was used as a CRI (1-5 mcg/kg/hr IV) and intermittent boluses throughout treatment in this case for sedation, anxiolysis, analgesia and muscle relaxation. Opioids can also be used to help control pain but patients should be closely monitored as these drugs can further enhance respiratory depression.[2] At the onset of clinical signs methadone was used for analgesia at 0.1 mg/kg IV q8h. As the patient's rigidity and spasms worsened he was started on a Fentanyl CRI (2-10 mcg/kg/hr IV). Gabapentin was also used for chronic and neuropathic pain in this case. Gabapentin (5-10 mg/kg PO q12h) may decrease calcium influx at voltage gated calcium channels inhibiting the release of excitatory neurotransmitters. Trazadone was also started in hospital and sent home with the patient. This serotonin antagonist reuptake inhibitor is used as an anti-anxiety medication. Oral methocarbamol (50 mg/kg q 8 h) was used later in the disease course when

spasms were less severe. Phenothiazines, such as acepromazine, reduce excitatory input on spinal cord lower motor neurons. It was successful later in this case in providing sedation and decreasing anxiety.[22]

Magnesium supplementation has been recommended in the treatment of tetanus cases as it is effective in enhancing muscle relaxation and controlling muscle spasms. Magnesium is beneficial as a non-specific calcium channel blocker. Magnesium decreases the sensitivity of the postsynaptic motor endplates to AcH which leads to muscle relaxation. One study reported after 16 hours of magnesium therapy, sedative medication was able to be decreased and the patient tolerated PROM exercises better. In the study, serum concentrations were kept at supraphysiologic levels between 4.63-8.34 mg/dL[5]. In this case, magnesium levels were not maintained at the recommended supraphysiologic levels (serum levels were maintained between 1.6-3.4 mg/dL) so it is impossible to conclude if the magnesium therapy helped control muscle spasms or decreased the need for additional medications in any way.

Intensive and supportive care is a vital part of treating the tetanus patient. Placing the patient in an environment with minimal stimulation will help slow the progression of disease. Comfortable bedding and constant rotation helps to prevent bed sores and atelectasis of the lungs. A urinary catheter may need to be placed to ensure the patient is able to urinate and for the quantification of urine production. Defecation should be monitored closely to avoid/prevent constipation. Tetanus patients are also in a hypermetabolic state so maintaining proper nutrition is critical. Placement of an esophagostomy or gastrostomy tube is necessary to maintain nutrition and body condition, though nasoesophageal or nasogastric tubes can also be used. Patients should be kept sternal while feeding or elevate their heads by 30 degrees once returned to their kennel to prevent gastroesophageal reflux. Studies have shown that early provision of nutrition results in a better prognosis for the patient. Physical therapy should also be started as soon as possible to ensure proper range of motion is achieved after treatment has ended.[2] Medical errors when managing an

intensive case, such as tetanus, sometimes occur. In the case described in this paper, two medical errors occurred during treatment. A bolus of magnesium was given resulting in serum levels of 5.5mg/dL. No treatment for this overdose was necessary. The patient was also given an overdose of dexmedetomidine. The reversal for dexmedetomidine, atipamazole was given and due to the lipophilic nature of dexmedetomidine, a dose of intravenous lipid therapy (1.5 mL/kg over 5 minutes, 0.25 mL/kg/min for 30-60 minutes) was given. Fortunately, these errors were realized quickly and the patient suffered no adverse events or side effects.

Treatment of tetanus can only be successful through the use of multiple treatment modalities and intensive supportive care and monitoring. This case used new therapies in the treatment of generalized tetanus including dexmedetomidine, gabapentin and trazadone. Areas for improvement in the treatment of future tetanus cases would be quicker administration of antitoxin at an increased dose, increased dose of magnesium sulfate throughout treatment, and increased provision of nutrition/caloric intake. Often the prognosis for generalized tetanus is grave due to the delay in diagnosis and the cost it takes to provide necessary treatment.[3] However, dogs who survive tetanus tend to have no residual effects and once well, lead normal, healthy lives.[23]

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