Focal tetanus involving both thoracic limbs successfully treated with magnesium sulfate in a dog

Focale tetanus van beide voorpoten succesvol behandeld met magnesiumsulfaat bij een hond

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ABSTRACT

A six-year-old, male, neutered Cocker spaniel was referred for a three-week history of progressive thoracic limb stiffness. The dog became non-ambulatory due to severe thoracic limb stiffness, which was exacerbated by external stimuli. The pelvic limbs appeared to be normal. Based on the history and the physical examination, a presumptive diagnosis of focal tetanus of the thoracic limbs was made. The dog was treated supportively with tetanus antitoxin, antimicrobials, sedation and muscle relaxants; however, this treatment did not control the muscle spasms adequately. Magnesium sulphate was added to alleviate the muscle spasms and to reduce the sedation requirements. The dog improved and was discharged after three weeks of intensive treatment.

SAMENVATTING

Een zes jaar oude, mannelijke, gecastreerde hond werd doorverwezen omwille van een stijve gang van de voorpoten. Het probleem startte drie weken eerder en werd geleidelijk aan erger. De hond kon niet meer zelf wandelen omwille van de erge stijfheid van de voorpoten. De spierkrampen werden erger door externe stimulatie. De achterpoten waren normaal. Een vermoedelijk diagnose van focale tetanus werd gesteld op basis van de anamnese en het lichamelijk onderzoek. De hond werd behandeld met antitetanus serum, antibiotica, sedatie en spierontspanners. Dit was onvoldoende om de spierkrampen voldoende onder controle te krijgen. Magnesiumsulfaat werd toegevoegd om de spierkrampen te bestrijden en om de hoeveelheid sedatie te verminderen. De toestand van de hond werd beter en hij verliet na drie weken intensieve behandeling de kliniek.

INTRODUCTION

Tetanus is a disease characterized by prolonged muscle contraction, through the action of the neurotoxin tetanospasmin. Tetanospasmin is produced by the gram-positive, obligate anaerobe bacterium *Clostridium tetani*. It comprises of two components – one that permits entry into nerve terminals and another that acts to enzymatically destroy synaptobrevin, a component of the synaptic vesicle docking apparatus. The classical signs of tetanus occur when the toxin binds irreversibly to presynaptic sites of inhibitory glycinergic and GABAergic interneurons, reducing their inhibitory effect on lower motor neurons and dramatically increasing muscle tone (Caleo and Shiavo, 2009). A persistent rigidity of a muscle group close to the site of injury is often the first abnormality detected in dogs with tetanus, which usually progresses to the rest of the body. Tetanus in domestic animals can present as a localized (focal) or generalized form. Localized tetanus is less common and usually the rigidity affects the limb closest to the wound (Penderis, 2012). Clinical signs of generalized tetanus include severe extensor rigidity, trismus and contraction of the muscles of facial expression (risus sardonicus); in severe cases, respiratory suppression and convulsions can develop (Rochelle et al., 2006; Admantos and Boag, 2007; Bandt et al., 2007; Burkitt et al., 2007).

It is easy to establish a diagnosis when the characteristic signs of tetanus are present. However, the diagnosis may not be obvious in those animals, in which the signs remain mild or localized, especially if there is no history or physical evidence of penetrating injury (Malik et al., 1989). Recovery from tetanus requires the formation of new axonal terminals and treatment relies on controlling increased muscle tone until this can be achieved. In this case report, an atypical presentation of severe focal tetanus is described, in which the dog had severe muscle rigidity in both thoracic limbs, without development of more generalized disease.

Figure 1. Photo of the dog at the time of admission in the hospital. Note the hyperextension of the thoracic limbs.

CASE

A six-year-old, male, neutered Cocker spaniel was referred for investigation of a three-week history of thoracic limb stiffness. Physical and neurological examination at that time was normal. Orthopedic examination revealed pain on extension of the elbow joints, with the right more severely affected than the left. The dog was discharged with meloxicam (Metacam® 0.1 mg/kg once daily) and exercise restriction. One week later, the dog was re-examined in the hospital due to progression of the thoracic limb stiffness. Physical examination revealed hyperthermia (39.8˚C), which was attributed to the increased muscle activity; there were no visible wounds or sources of potential infection. The remainder of the general physical examination was unremarkable. On neurological examination, the dog was non-ambulatory due to markedly increased extensor muscle tone in the thoracic limbs; the pelvic limbs appeared normal (Video 1: https://vimeo.com/377558260 and Video 2: https://vimeo.com/377558180) (Figure 1). Passive flexion of the thoracic limbs could not be performed and postural reactions and withdrawal reflexes could not be elicited due to the severe spasticity; this was worsened by environmental stimuli (sounds, sudden movements). Nociception was intact in both thoracic limbs. The pelvic limbs were perceived to be normal, with intact postural responses and spinal reflexes. The dog had an appropriate mental status and cranial nerve examination was normal. Based on the neurological examination, neuroanatomical localization was within the upper motor neuron system of the thoracic limbs, more likely C1-C5 spinal cord segments, although the lack of involvement of the pelvic limbs was difficult to explain. Further diagnostic investigation was performed.

Hematology was unremarkable. Comprehensive biochemistry revealed a moderate increase in creatine kinase (CK 2796 U/L (0-190)) and a mild increase in aspartate aminotransferase (AST (130 U/L (0-49)). Magnetic resonance imaging (MRI) of the brain, the cervical vertebral column and the brachial plexi was performed under general anesthesia and revealed no significant abnormalities. The muscle tone of the thoracic limbs improved but remained increased under general anesthesia. A cisternal cerebrospinal fluid (CSF) sample also revealed no abnormalities. Electromyography (EMG) of the muscles of the thoracic and pelvic limbs was performed under general anesthesia, revealing no abnormal electrical activity. On the basis of the history and the results of these examinations, the clinical diagnosis of localized tetanus was made.

The dog was hospitalized in a darkened and quiet room. Treatment was initiated with antitetanus equine serum (Tetanus Antitoxin Behring® 500 IU/kg, MSD Animal Health, Ireland), initially with 0.1 ml (100 IU) given subcutaneously (SC), followed by a full dose of tetanus antitoxin given intravenously (IV), slowly over thirty minutes. A course of metronidazole was started (10 mg/kg twice daily oral (PO) for 14 days) and medication to control muscle spasticity was instigated, initially consisting of midazolam boluses (0.1-0.2 mg/kg IV), given when necessary, combined with oral methocarbamol (60 mg/kg every 8 hours PO). Acepromazine (ACP) (0.01 mg/kg every 4-6 hours IV) was started on day 1 to reduce excitability, with buprenorphine (0.02 mg/kg every 6-8 hours IV) and paracetamol (10 mg/kg every 12 hours IV) for analgesia. The dog was fed as normal during the entire hospitalization period, with a dose of midazolam (0.1 mg/kg IV bolus) given ten minutes before feeding, if necessary. The vital parameters were monitored every 4-6 hours or more frequently, if required.

During the first week, there were increasing muscle spasms combined with myoclonic jerks, periods of agitation and hypersensitivity to external stimuli. A continuous rate infusion (CRI) of dexmedetomidine (1-2 microgram/kg/hour) was started on day 2 to reduce the excitability. On day 4, midazolam treatment was changed to a constant rate infusion (0.1-0.6 milligram/kg/hour) and on day 5, dantrolene (2 mg/kg every 12 hours PO) was added. Despite this, the muscle spasms and hyperexcitability persisted. To address this, treatment with magnesium sulphate ($MgSO_4$) was started on day 5, with the goal being to increase the total serum magnesium concentration to 2-4 mmol/L (normal reference range: 0.6-1.2

mmol/L) (Attygalle and Rodrigo, 2002). The dog was initially treated with a loading dose of 70 mg/kg over thirty minutes, following which a CRI was initiated at 30 mg/kg/hour. The serum magnesium concentrations were monitored every 4-6 hours the first day and later on a daily basis, with the infusion rate being adjusted between 30-45 mg/kg/hour accordingly. The patellar reflex was assessed hourly for signs of hyporeflexia, an early indicator of toxicity (Attygalle and Rodrigo, 2002). Asymptomatic, mild hypocalcemia (ionized Ca 0.94-1.08 mmol/L (normal reference range: 1.25-1.50 mmol/L)) was attributed to the $MgSO_4$ treatment and was left untreated (Attygalle and Rodrigo, 2002). On day 7, the dexmedetomidine CRI was stopped and on day 10, the ACP boluses were also discontinued. After two weeks of intensive treatment, the dog started improving, with the muscle spasms and hyperexcitability becoming less severe (Video 3: https://vimeo.com/377558214). The midazolam CRI was tapered gradually and finally discontinued on day 15, whilst the $MgSO_4$ was tapered and discontinued on day 20. On day 21, the dog was able to ambulate unaided, with some residual thoracic limb stiffness; he was discharged home two days later, with oral methocarbamol (Penderis, 2012). At the follow-up examination twelve months after hospitalization, the dog was found in good health, having made a complete recovery.

DISCUSSION

Although a similar case has been described in the literature, this atypical form of focal tetanus is extremely rare and not well known amongst veterinary surgeons (De Risio et al., 2006). The description of the clinical signs together with the videos of this case will help to increase the awareness of this atypical form of focal tetanus amongst veterinary professionals. Recognition of the symptoms in an early stage of the disease will result in less unnecessary diagnostics and in earlier intervention, such as wound debridement, administration of antibiotics and antitoxin administration, which can prove crucial for a successful outcome. To the authors' knowledge, this is the first report of the use of $MgSO_4$ to treat focal tetanus in a dog. Treatment with $MgSO_4$ has been described in one dog affected by generalized tetanus (Simmonds et al., 2011). A higher starting dose of $MgSO_4$ was used in this case in order to reach therapeutic concentrations faster. This treatment protocol with $MgSO_4$ can be used for future reference in dogs diagnosed with focal or generalized tetanus.

The neurological signs in the case documented here are unusual. Most dogs with tetanus present with changes in facial expression and generalized muscle hypertonicity; and the diagnosis is commonly reached based on clinical signs alone. Focal tetanus is an unusual manifestation of tetanus. By definition, this form is limited to the muscles of the wound site. This is thought to occur when circulating antitoxin neutralizes the tetanus toxin. However, the antitoxin does not prevent the spread of tetanus toxin along the regional neurons. Focal tetanus is characterized by spasms of the muscles adjacent to the wound site, which usually worsen with external stimuli (Moodley and Jones, 2003; Penderis, 2012). History or physical evidence of a penetrating injury supports the diagnosis but is not always present, which makes the diagnosis of focal tetanus more challenging (De Risio et al., 2006). In some cases, confirmation can be verified by the isolation of *C. tetani* from an infected focus. However, this is unrewarding in the majority of cases since the organism concentration is usually low and culture has to be performed under strictly anaerobic conditions (Struppler et al., 1963; Weinstein, 1973). Moreover, a wound is often not identified in affected patients, since the incubation period in dogs may be up to three weeks, by which time the primary wound has healed (Greene, 1998). Recognition of the clinical syndrome is therefore crucial in reaching a prompt diagnosis and instigating treatment.

Although the signs were focal in the current case, the marked increase in muscle tone and hyperreactivity to external stimuli were strongly suggestive of focal tetanus. However, given the unusual presentation – and in the absence of a wound to confirm a plausible source of infection – various ancillary tests were carried out to exclude other possible causes of the presenting signs. This failed to yield a significant lesion and the dog was therefore diagnosed with focal tetanus. Determining the presence of anti-tetanus antibody titres was considered but previous reports have indicated this is of no use in localized tetanus as insufficient toxin is produced to trigger a measurable antibody response (Struppler et al., 1963; Weinstein, 1973).

EMG may help to confirm the diagnosis of focal tetanus (Jain et al., 1982; Malik et al., 1989; Polizopoulou et al., 2002; De Risio et al., 2006). The presence of persistent motor unit activity during rest and general anesthesia is supportive of a diagnosis of focal tetanus. This activity reflects the spontaneous firing of disinhibited motor neurons (Jain et al., 1982; Malik et al., 1989; Polizopoulou et al., 2002; De Risio et al., 2006). The EMG findings in focal tetanus have only been described in two dogs (Malik et al., 1989; De Risio et al., 2006). In one dog with focal tetanus of the thoracic limbs, conscious EMG showed continuous spontaneous motor unit discharges (De Risio et al., 2006). In the other case, a dog with focal tetanus affecting the right thoracic limb, EMG performed under general anesthesia demonstrated spontaneous motor unit potentials in the lateral head of the triceps muscles (Malik et al., 1989). In the current case, EMG under general anesthesia revealed no spontaneous electrical activity.

Treatment of tetanus is based on controlling clini-

cal signs, predominantly muscle spasms, whilst new inhibitory synapses are formed. This typically requires a range of different drugs, which target different components of the physiological pathway of muscle fibre contraction. Despite using a variety of drugs, many patients with tetanus continue to suffer severe muscle spasms, rendering management challenging. Magnesium sulphate has been used in human patients with tetanus to aid in reducing muscle spasms (Attygalle and Rodrigo, 2002). The beneficial effects of magnesium in a tetanus case are most likely multifactorial. Magnesium acts as a non-specific calcium channel blocker, reducing release of acetylcholine at the neuromuscular junction (Simmonds et al., 2011). Magnesium also decreases the release of catecholamines from the adrenal glands and the peripheral adrenergic nerve terminals (Douglas et al., 1963). So far, there is only one case report in the veterinary literature in which the use of $MgSO_4$ to treat tetanus in a dog has been described (Simmonds et al., 2011); however, from clinical experience, $MgSO_4$ is increasingly used in the management of cases with tetanus in veterinary practice.

The aim of using $MgSO_4$ is to increase the total serum magnesium concentration to 2-4 mmol/L, a figure based on a target therapeutic range derived from human medicine (Attygalle and Rodrigo, 2002). In humans, an intravenous magnesium infusion is started with a loading dose of 75-80 mg/kg over thirty minutes followed by a maintenance dose of 2 g/hour (28 mg/kg/hour for a person weighing 70 kg) if aged under 60, and 1 g/hour (14 mg/kg/hour for a person weighing 70 kg) if aged 60 or elderly (Attygalle and Rodrigo, 2002). In the present case, a similar loading dose was used followed by an infusion at a rate of 30 mg/kg/hour, which resulted in the target therapeutic concentration being reached in 24 hours. The following day, the dose of the medetomidine CRI could be reduced and was then tapered further and stopped one day later. In the only available veterinary case report, lower doses of $MgSO_4$ were used (Simmonds et al., 2011), with an initial CRI of 4 mg/kg/hour, subsequently increased to 15-20 mg/kg/hour to achieve concentrations between 2 and 4 mmol/l (Simmonds et al., 2011). In the patient in the present report, higher doses were used from the beginning based on previous experience indicating the need for higher dose rates than reported. Generally, better control of the muscle spasms requires less sedation, which reduces nursing care and monitoring. This also reduces the cost of hospitalization and the workload for the nursing staff.

However, supraphysiological magnesium therapy carries the risk of toxicity. Reported signs and symptoms of magnesium toxicity in humans range from lethargy and nausea to respiratory depression, coma and cardiac arrest (Attygalle and Rodrigo, 2002; Simmonds et al., 2011). Deep tendon hyporeflexia is one of the earliest signs of magnesium toxicity (Attygalle and Rodrigo, 2002; Simmonds et al., 2011) and testing the patella tendon reflex is therefore an easy way to monitor for possible magnesium-associated toxicity. In the current case, no clinical signs of magnesium toxicity were observed. Asymptomatic hypocalcemia was noted but this is a common finding in humans treated with $MgSO_4$ (Attygalle and Rodrigo, 2002) and does not appear to require specific treatment.

CONCLUSION

In this case report, an atypical presentation of focal tetanus is described. The history, clinical presentation and ancillary tests supported the diagnosis of focal tetanus. Severe focal tetanus can be treated successfully with intensive supportive treatment, and magnesium may play a useful role in the treatment of this disease.

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Ook de 'Spaanse griep' (1918-1919) was een zoönose

Wellicht de meest dodelijke pandemie die de menselijke soort ooit trof, was de zogenaamde Spaanse griep, die opdook in de laatste maanden van de Eerste Wereldoorlog, tijdens de zomer van 1918. De epidemie hield aan tot 1919. Opvallend was dat de ziekte vooral jongvolwassenen trof.

Lange tijd bleef de oorzaak een raadsel. Men wist enkel dat het een 'filtreerbaar agens' betrof: een virus dat ernstige, vaak dodelijke griepsymptomen opwekte en uiterst besmettelijk was. Er was niets Spaans aan, behalve het feit dat het ongecensureerde kranten uit het neutrale Spanje waren die het nieuws over de ziekte uitbrachten.

Virusisolaten uit de jaren dat deze griep heerste, waren niet voorhanden: de virologie was toen nog embryonaal. Maar toch bleef er voldoende bewaard om (veel later) klaarheid te brengen. Naast genetisch materiaal uit de permafrost (permanent bevroren aardlagen) werd ook virus teruggevonden in paraffineblokjes met longweefselcoupes van overledenen. Het is dus het genetisch materiaal dat bewaard bleef, niet het virus zelf. Men kon daarmee door "reverse genetics" het oorzakelijke virus kunstmatig en theoretisch reconstrueren.

De oorzaak van de Spaanse griep was waarschijnlijk een volledig aviair influenzavirus, geen recombinant, zo bleek. Volgens beschikbare bronnen werd het virus overgedragen van wilde watervogels op mensen. Alle influenzavirussen pandemisch bij mensen woekerend in 1918, 1957, 1968 en 2009 waren zoönotisch in oorsprong. Meestal vormden vogels het virusreservoir. In 2009 speelde het varken wel een rol.

Net als de meer recente griepepidemieën en ook Covid 19 was Spaanse griep dus een zoönose, niet in de zin dat mensen in regel door dieren of dierlijke producten besmet werden, maar dat een virusreservoir bij dieren aan de oorsprong lag van de eerste menselijke infecties die dan verder van mens tot mens overgezet werden.

Wellicht niet toevallig werd het begrip kiemreservoir geïntroduceerd in de infectiologie door een dierenarts: Karl Friedrich (gemeenzaam K.F.) Meyer (zie VDT 2020 nr. 2, p. 120). Deze geboren Zwitser, die onderzoek deed in Zuid-Afrika en de VSA en ook aan de basis lag van de ontdekking van de mycoplasmen en van het fenomeen 'latente infectie', was in meer dan één opzicht een monument.

Luc Devriese

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