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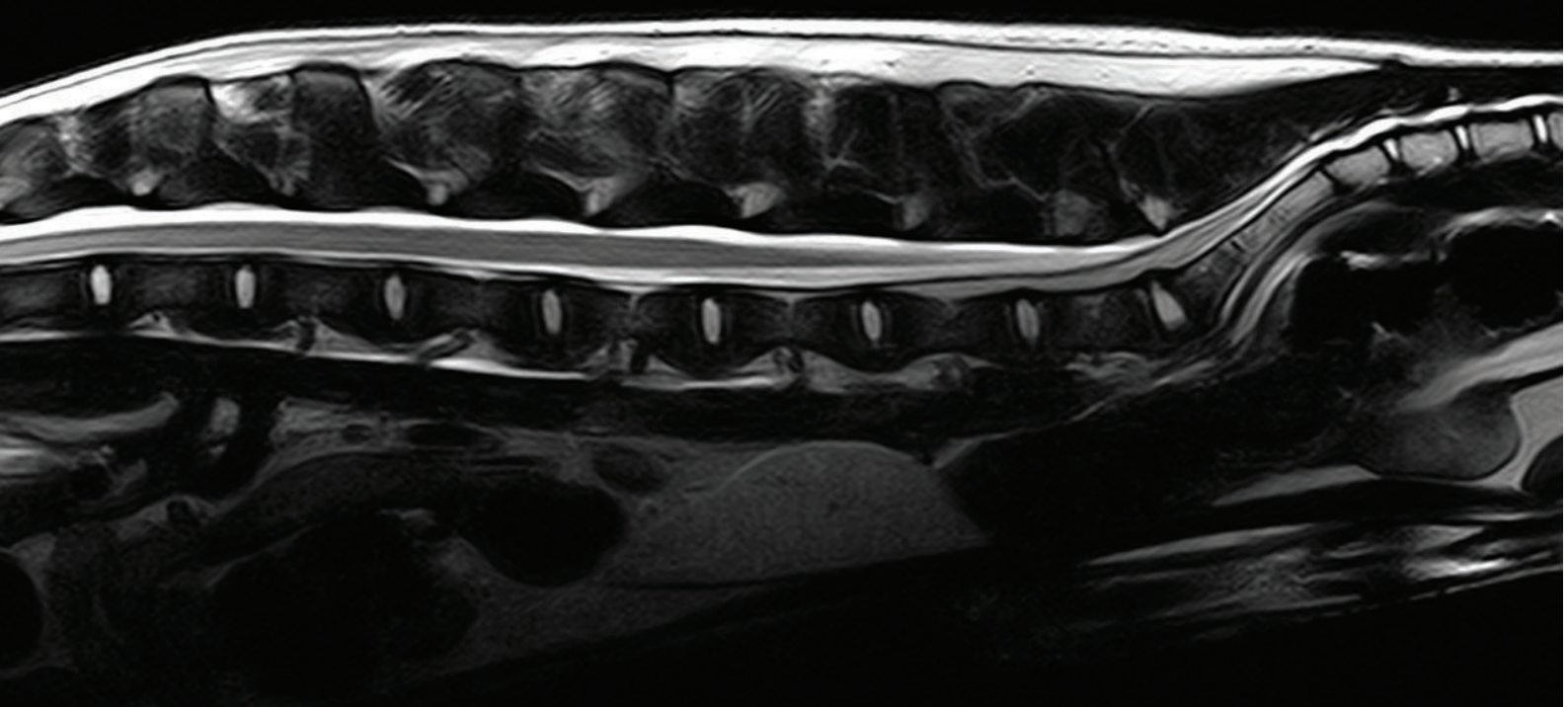

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STANDARD ARTICLE

Association between clinically probable REM sleep behavior disorder and tetanus in dogs

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Background: Abnormal sleep behavior has been reported in 5 dogs during recovery from tetanus.

Hypothesis: REM sleep behavior disorder (RBD) is a more common consequence of tetanus than previously reported in veterinary literature and easily confused for epileptic seizures.

Animals: Sixty-one client-owned dogs diagnosed with tetanus at 2 UK referral centers.

Methods: A retrospective review of medical records was combined with a questionnaire sent to owners of surviving dogs, to identify cases that developed clinically probable RBD and determine its clinical progression and effect on quality of life of affected dogs and their owners. Descriptive statistical evaluation was performed.

Results: Eleven dogs (18%) died or were euthanized before discharge. At least 46% surviving dogs developed abnormal "dream enactment" clinically consistent with RBD. Twitching, running, and vocalization were new sleep behaviors in 53, 80, and 60% of affected dogs. Clinically probable RBD was described as violent or "nightmare"-like in 36% affected dogs, and like an epileptic seizure in 40% affected dogs. When trialed, antiepileptic medications were ineffective. Onset occurred before discharge in 25% cases. For dogs that developed clinically probable RBD post-discharge, onset occurred within 2 weeks of discharge in 77% dogs. Clinically probable RBD did not worsen in severity or frequency in any dog, and spontaneously resolved within 6 months in 43% cases.

Conclusions and Clinical Importance: Clinically probable RBD is a common sequel to canine tetanus with many clinical similarities to epileptic seizure activity. Owners should be made aware of its potential development and care taken to avoid misdiagnosis with epileptic seizure activity.

KEYWORDS

canine, *Clostridium tetani*, dog, REM sleep behavior disorder, seizure, tetanus

1 | INTRODUCTION

Tetanus is a disease that results from the irreversible binding of tetanospasmin toxin C (produced by the Gram-positive anaerobic spore-forming bacillus *Clostridium tetani*) to presynaptic sites on inhibitory neurons. This binding inhibits the release of the inhibitory neurotransmitters glycine and γ-aminobutyric acid (GABA), resulting in sustained, rigid contraction of muscles.[1] In addition to muscular spasms, epileptic seizure activity can also occur—likely because of the loss of inhibitory function. Recovery from tetanus is dependent on the production of new axonal terminals which can take weeks to months.[2] Complete resolution of epileptic seizure activity might occur, with discontinuation of antiepileptic medication possible in these cases.[3]

There is limited published data in the veterinary literature, with 3 case series (of 13,[3] 20,[4] and 38[5] dogs) and multiple single case reports of tetanus in dogs. The case series have tended to focus on risk factors for recovery and outcome with 2[3,5] also reporting on long-

Abbreviations: q12h, twice daily dosing; cpRBD, clinically probable REM sleep behavior disorder.; CRI, continuous rate infusion.; EEG, electroencephalography.; RBD, REM sleep behavior disorder.; REM, rpid eye movement.

term outcome. In 1 case series, 3 (8%) dogs were reported to have sleep-associated disorders at 6 and 12 weeks after recovery from tetanus, consisting of persistent muscular spasms that were hypothesized to be the result of permanent damage to inhibitory neurocircuits.[5] No further information was provided regarding these signs. Two case reports have also recorded post-tetanus sleep-associated disorders.[6,7] All dogs affected by these abnormal sleep behaviors had exhibited generalized signs of tetanus.

Normal sleep comprises of a continuous cycle through 2 phases: the initial nonrapid eye movement phase characterized by immobility with retention of muscle tone, and the rapid eye movement (REM) phase which is characterized by an alert state of brain activity, REM and atony of the major limb muscles. While normal animals might display a degree of twitching and vocalization during REM sleep (commonly interpreted as manifestation of dream activity), loss of the normal inhibition of select lower motor neuron ventral horn cells results in violent limb movements and potentially aggressive behavior during this phase of sleep. This abnormal and excessive manifestation of dream activity is termed REM sleep behavior disorder (RBD).[8–10] A clinical diagnosis of RBD requires (1) repeated episodes of behavior or vocalization that are either documented by polysomnography to arise from REM or are presumed to arise from REM based on reported dream enactment, and (2) evidence of REM sleep without atonia on polysomnography.[11] In cases where polysomnography is not performed a provisional diagnosis (clinically probable RBD) can be made if clinical findings are strongly suggestive.

We hypothesized that RBD is a more common consequence of generalized tetanus than previously reported in the veterinary literature and can be confused for epileptic seizure activity. The primary aim of this retrospective study was to further investigate the prevalence, clinical features, and severity of clinically probable RBD (cpRBD) as a complication of tetanus. In addition, the study aimed to determine whether this complication is truly permanent, whether antiepileptic medications (should these have been trialed) overtly reduced the severity/frequency of episodes, and the effect of the disorder on the quality of life of the dog and the owner.

2 | MATERIALS AND METHODS

This study was approved by the ethical committees of both participating institutions. Dogs with a presumptive diagnosis of tetanus presenting between January 2000 and April 2017 were identified from the databases of 2 UK veterinary referral centers. Cases were included if their clinical signs (including risus sardonicus, erect ears, protrusion of the third eyelids, trismus, and rigidity of multiple muscles with worsening of clinical signs at times of stimulation), history and clinical progression (progressive development of the above clinical signs over days to weeks, with an identified potential source of infection deemed supportive) were consistent with tetanus, with diagnostic investigations including comprehensive serum biochemistry profiles and blood gas analyses excluding other causes of tetany (eg, secondary to hypocalcemia [total calcium <6.0 mg/dL {<1.5 mmol/L}; ionized calcium <0.8 mmol/L], hypokalemia [<2.5 mEq/L {<2.5 mmol/L}], acidosis [<7.20] and alkalosis [>7.55], and hypomagnesemia [<0.61 mg/dL {<0.25 mmol/L}] where measured). Isolation of *C. tetani* from identified wounds was not necessary for inclusion of dogs in this study.

Data extracted from the medical records included signalment, history, information regarding clinical signs and their progression, treatment, duration of hospitalization, whether a sleep disorder was noted during the hospitalization period and if attempts were made to wake the dog, whether electroencephalographic (EEG) recording was performed during these episodes, and the presence/absence of epileptic seizure activity during hospitalization. Questionnaires (see Supporting Information) were subsequently sent to the owners of eligible survivors to identify dogs that subsequently developed cpRBD, and to evaluate the features, progression, response to treatment, and its effect on the quality of life of both the dog and their owner. Sleep behavior before the development of tetanus was also evaluated. When available, video footage of the episodes was reviewed.

Descriptive statistical analysis (median, mean, SD, range) was performed on data collected from medical records and the owner-completed questionnaires.

3 | RESULTS

Sixty-one dogs met the inclusion criteria; 33 were male (20 entire, 13 neutered) and 28 were female (11 entire, 17 neutered). The median age at presentation was 3.5 years (mean 3.78 ± 2.77; range 0.25-10.4). Labradors were the most common breed (14/61; 23%), followed by crossbreeds (12/61; 20%), Border Collies (4/61; 7%), Staffordshire Bull Terriers (4/61; 7%), Cocker Spaniels (4/61; 7%), English Springer Spaniels (3/61; 5%), Pointers (2; 3%), Dobermanns (2/61; 3%) and 1 each of Lurcher, Pug, Rhodesian Ridgeback, Munsterlander, Weimaraner, Golden Retriever, American Bulldog, Scottish Terrier, English Bull Terrier, Italian Spinone, Norfolk Terrier, and American Cocker Spaniel. The median body weight at presentation was 22.2 kg (mean 22.5 ± 9.44; range 4.45-50).

Generalized signs of tetanus were evident in 55 dogs (90%) whereas 6 (10%) displayed only focal (all involving only the muscles of the head) tetanus throughout their illness. A wound or other source of infection was identified in 58/61 (95%) dogs, with a total of 63 sites of infection identified (2 dogs had 2 wounds, 1 dog had 3). The thoracic limbs were most commonly affected with 34/63 (54%) sites of infection; digital wounds/nail bed infections were the most common site (21/34; 62%). Twelve (19%) wounds were identified in the pelvic limbs, with digital wounds/nail bed infections counting for half of these. A further dog was reported to have a paw wound and a nail bed infection however the affected limb was unclear from its records. The affected digit(s) were radiographed in 23 dogs with digital wounds/nail bed infections: 11/20 thoracic limb and 3/3 pelvic limb digits exhibited radiographic evidence of osteomyelitis. Nine (14%) wounds/sources of infection were identified in the oral cavity, with 6/9 (67%) associated with teeth. The remaining sites were the thorax (1/63; 2%), abdomen (3/63; 5%—including 1 intra-abdominal [post-ovariohysterectomy] case) and head (2/63; 3%). *Clostridium* species were cultured from 4/12 (33%) cultured wounds. For 10 of these cases, dogs were already receiving antibiotics at the time of culture, including 2/4 dogs with clostridial growth. The median duration

between identification of a wound/source of infection and onset of clinical signs of tetanus was 12.4 days (mean 15.2 ± 5.49; range 0-30).

The median duration between onset of clinical signs to presentation at the referral hospital was 4.0 days (mean 4.6 ± 4.10; range 0.5-30). All dogs were subsequently treated with appropriate antibiotic therapy (metronidazole, penicillin G, and/or doxycycline), analgesia and muscle relaxants. Tetanus antitoxin, wound debridement/digit amputation and further supportive care (urinary catheterization, intravenous fluid therapy, feeding tube placement, gastrointestinal protectants, physiotherapy, ocular and oral lubrication, suctioning of airways, rotation of recumbency, oxygen supplementation, tracheostomy tube placement, and mechanical ventilation) were administered as necessary at the discretion of the primary clinician. Table 1 summarizes the main targeted treatments: in addition, 4 dogs received continuous rate infusions (CRI) of magnesium sulfate, 34 dogs received acepromazine, 28 dogs received a non-steroidal anti-inflammatory, 7 dogs received a corticosteroid, 13 received an opioid, and 8 received another form of analgesia (paracetamol, tramadol, gabapentin, lidocaine CRI). Propofol and (dex)medetomidine CRIs were administered in 6 cases each; for each treatment, 4 dogs were in the cpRBD group and 2 dogs died. An in-dwelling urinary catheter was placed in 13 dogs; 9 dogs developed cpRBD, 1 dog did not, and the remaining 3 dogs died. Mechanical ventilation was required in 2 dogs; both subsequently died.

One dog was not hospitalized; for the remaining dogs, clinical signs progressed during hospitalization in 27/60 (45%) dogs. Eleven dogs (18%) died or were euthanized during hospitalization due to clinical deterioration; 3 dogs were euthanized on the grounds of welfare, 2 were euthanized due to a combination of severe clinical deterioration and financial constraints, and 6 died of cardiopulmonary arrest secondary to respiratory dysfunction (including respiratory tract obstruction secondary to increased respiratory secretions and aspiration). The median survival time from onset of clinical signs and admission to the referral practice were 7.5 (mean 6.9 ± 3.04; range 2-11) and 5.0 (mean 4.4 ± 2.51; range 1-9) days, respectively. The median duration of hospitalization for survivors was 9.0 days (mean 11 ± 8; range 0-30). Questionnaires were returned for 25 of the 50 surviving dogs (50%) although not all questions were answered in every case.

Based on medical records alone (3 dogs) and combined medical records and owner-completed questionnaires (20 dogs), a change in sleep behavior was reported in 23 dogs (see Supporting Information). All but 1 dog was affected by generalized tetanus. When attempted, all dogs were easily woken from the episodes. Electroencephalographic recording during these episodes was not obtained in any dog, however, based on overt dream enactment, ease of waking, a lack of autonomic and post-ictal signs, and failure to respond to antiepileptic medications when trialed, these episodes were considered consistent with cpRBD.

Clinically probable RBD was first noted during hospitalization in 5/23 (22%) dogs, with the abnormal sleep behavior noted post-discharge by their owners in the remaining 18/23 (78%) dogs. Only 5 dogs were reported to have never developed abnormal sleep behavior; the presence/absence of cpRBD was unknown in 22 dogs. Therefore, at least 23/50 (46%) dogs developed cpRBD during their recovery from tetanus.

For dogs with onset after discharge, cpRBD reportedly occurred during the first day/night after discharge (4/9; 44%), or within days (1/9; 11%), 1 week (1/9; 11%), 1-2 weeks (1/9; 11%), <2 months (1/9; 11%), or >2 months (1/9; 11%) of discharge. Episodes consistent with cpRBD occurred every time the dog slept in 5/18 (28%) cases, at least once per day in 3/18 (17%) dogs, several times per week in 3/18 (17%) dogs, once a week in 2/18 (11%) dogs, several times per month in 2/18 (11%) dogs, and once a month in 1/18 (6%) dogs. For the remaining 2 dogs (11%), the owners were unsure of the frequency of cpRBD.

Clinically probable RBD manifested as twitching (21/23; 91%), running movements (19/23; 83%), vocalization (17/23; 74%), and jaw chomping (8/17; 47%; refer to the Supporting Information). For the dogs in which sleep behavior before the development of tetanus was known, 5/16 (31%) dogs had never been seen to display any of these movements and a further 10 (63%) dogs displayed new/different sleep behaviors after tetanus. Twitching, running movements, and vocalization manifested for the first time after tetanus in 8/15 (53%), 12/15 (80%) and 9/15 (60%) dogs, respectively. In dogs that had displayed running movements pre-tetanus, the degree of movement increased in 7/9 (78%) dogs. While no dogs were themselves hurt (although 1 was reported to have fallen from the sofa during cpRBD), in 3/20 (15%) cases a human was bitten during an episode with 1 dog's owner requiring hospitalization for bite wound treatment.

The severity of cpRBD was subjectively graded by owners as mild in 7/19 (37%), moderate in 8/19 (42%), and severe in 4/19 (21%) dogs. The episodes were described by owners or members of staff as "violent" or a "nightmare" in 7/20 (35%) dogs, and like an epileptic seizure in 8/20 (40%) dogs. Despite 12/19 (63%) owners subjectively considering the cpRBD to be moderate or severe, only 1/19 (5%), 4/19 (21%), and 1/19 (5%) owners felt they needed to wake their dog from these episodes quite often, very often or every time, respectively. The owners of 8/19 (42%) never woke their dog, with the remaining owners only occasionally feeling they needed to wake their pet. On waking, 11/16 (69%) dogs were reported to be normal and 5/16 (31%) dogs initially appeared disorientated or confused.

For 14/17 (82%) dogs, the cpRBD had no perceivable impact on their quality of life according to their owner. Quality of life was subjectively considered minimally and mildly impaired in 1/17 and 2/17 dogs, respectively, with no dog perceived to have a moderately or markedly worse quality of life. While 14/16 (88%) and 1/16 owners felt their own quality of life was not or minimally impaired, 1/16 owners reported a marked impact on their own quality of life as a result of their dog's cpRBD.

The frequency of the cpRBD improved in 9/17 (53%) dogs. Where it was known, this improvement occurred within 1-2 weeks in 3/6 (50%) dogs and within 6 months for the remaining 3. The severity of cpRBD episodes improved in 8/15 (53%) dogs. In the cases for which it was known, this improvement occurred within 1-2 weeks or 1-2 months in 2/5 (40%) dogs each. In the remaining dog, improvement in episode severity was noted between 2 and 6 months after onset. The cpRBD episodes resolved in 7/16 (44%) dogs, with a return to normal sleep behavior within 1-2 weeks (1/6; 17%), within 1 month (2/6; 33%), between 1 and 2 months (1/6; 17%) or between 2 and

TABLE 1 The main targeted treatments administered to dogs with tetanus (n indicates the number of dogs that received the treatment; *days post-onset* refers to the number of days after the onset of clinical signs of tetanus that the treatment was performed)

	Dogs with cpRBD			Dogs without cpRBD			Nonsurvivors			All survivors		
Treatment administered	**Median**	**Mean (SD)**	**Range (n)**	**Median**	**Mean (SD)**	**Range (n)**	**Median**	**Mean (SD)**	**Range (n)**	**Median**	**Mean (SD)**	**Range (n)**
Antibiotics (days administered)												
Metronidazole	27.5	22.8 (8.2)	10-32 (22)	31.5	42.3 (38.5)	12-94 (5)	6.5	6.3 (3.0)	2-10 (7)	18	22 (16.1)	8-94 (49)
Amoxicillin-clavulanic acid	22	20.1 (9.0)	7-32 (14)	37	43.0 (34.0)	10-88 (5)	1.5	3.5 (3.7)	1-10 (8)	22	22.3 (18.2)	4-88 (29)
Penicillin G	5.5	5.5 (6.1)	1-10 (2)	0	0	0 (0)	2	2 (0)	2 (2)	3	6.5 (7.8)	1-21 (8)
Muscle relaxants (days administered)												
Midazolam CRI	6	6.6 (4.9)	2-13 (10)	Unknown	Unknown	Unknown (1)	6.5	6.0 (1.4)	4-7 (4)	6	6.6 (4.9)	2-13 (11)
Diazepam	13	12.1 (10.5)	2-33 (10)	12	13.3 (8.1)	6-22 (3)	2	2 (0)	2 (2)	12	13.3 (11.2)	2-44 (21)
Methocarbamol	23	22.5 (7.0)	14-30 (12)	21.5	21.5 (10.6)	14-29 (2)	3.5	3.5 (3.5)	1-6 (2)	19	20.1 (7.5)	10-30 (17)
Anti-toxin												
Dose (IU/kg)	377	410.8 (292.1)	100-1000 (14)	500	416.7 (144.3)	250-500 (4)	100	131.0 (80.1)	71-222 (6)	254	327.3 (256.1)	17-1000 (29)
Days post-onset	3	3.1 (1.7)	1-7	5	4.8 (2.1)	2-7	5	4.1 (1.9)	2-7	4	4.0 (2.0)	1-8
Digit amputation/wound debridement												
Days post-onset	4.5	5.8 (3.1)	4-12 (10)	6.5	6.5 (2.1)	5-8 (2)	7.5	7.5 (0.7)	7-8 (2)	6	6.1 (2.9)	1-12 (18)
Days after wound first noticed	9.5	11.6 (3.7)	8-15	7.5	7.5 (10.6)	0-15	12	12 (0)	12	12.5	11.9 (6.1)	0-26
Feeding tube												
Days in place	18	15 (6.9)	7-26 (15)	7	11.3 (10.2)	4-23 (3)	3.5	4 (2.1)	2-7 (7)	12	14 (7.5)	4-27 (29)
Days placed post-onset	4	5.5 (3.0)	1-12	8	9 (3.6)	6-13	5	4.7 (2.3)	2-8	5	5.7 (2.9)	2-13
Tracheostomy tube												
Days in place	17.5	17.5 (0.7)	17-18 (2)	0	0	0 (0)	2.5	2.5 (0.7)	2-3 (3)	12.5	12.3 (6.1)	6-18 (4)
Days placed post-onset	3	3 (0)	3	0	0	0	7	7.0 (2.0)	5-9	3	3.75 (1.5)	3-6

TABLE 2 Comparison of potential clinical severity measures between dogs with and without clinically probable RBD after tetanus

	Dogs with cpRBD (n = 23)			Dogs without cpRBD (n = 5)		
	Median	Mean (SD)	Range	Median	Mean (SD)	Range
Time from identification of wound to onset of clinical signs (days)	7	6.3 (2.08)	2-10	9	10.3 (4.16)	7-15
Time from onset of clinical signs to presentation (days)	3	4 (2.73)	1-14	7	6.2 (1.64)	4-8
Duration of hospitalization (days)	15	14 (8)	1-30	6	10 (8)	4-23

6 months (2/6; 33%) after onset. Neither frequency nor severity worsened in any dog.

Trial treatment was attempted with antiepileptic medications (AEDs) in 6/23 dogs. Medications administered included phenobarbitone (n = 5; at 2-3 mg/kg q12h [with 1 dog receiving a loading dose] for 19-57 days [median and mean of 38 days, SD 26.9]), levetiracetam (n = 2; at 10-20 mg/kg for 15 days each), and potassium bromide (n = 1; loading dose then 40 mg/kg/day for 60 days). No perceived response to AED treatment was noted in any dog.

Based on medical records and completed questionnaires, only 5/50 dogs are known to have not developed cpRBD during their recovery from tetanus. Because of the low case numbers statistical evaluation of cpRBD and non-cpRBD cases to determine potential risk factors was not possible. However, while sex, age, and weight at diagnosis were similar between the 2 groups, 5/12 (42%) surviving Labradors and 2/3 (67%) surviving Cocker spaniels developed cpRBD while neither of these breeds were represented among the dogs known to have not. The time from identification of a wound/source of infection to development of clinical signs and from onset of clinical signs to presentation at a referral center tended to be longer, and duration of hospitalization tended to be shorter, in dogs that did not develop cpRBD (Table 2). The number of dogs that exhibited progression of their clinical signs during hospitalization was similar between groups (10/23 (44%) dogs with cpRBD versus 2/5 (40%) dogs without reported cpRBD). Pre-tetanus sleep behavior appeared similar between groups (Tables 3 and 4), however 3/19 (16%) dogs with post-tetanus cpRBD were considered by their owners to have overtly "dreamt" more than other dogs pre-tetanus while no dogs without cpRBD were considered to have "dreamt" more than other dogs.

4 | DISCUSSION

While abnormal sleep behavior has previously been reported in dogs recovering from tetanus,[5–7] at least 46% of dogs in our study displayed episodes consistent with clinically probable RBD, suggesting this to be a far more prevalent sequel of tetanus than previously thought. To the authors' knowledge, RBD/cpRBD has not been reported as a consequence of tetanus in any other species; however, 1 human study reported 6 patients who complained of sleep disturbance (difficulty falling asleep, frequent waking during the night and frequent, terrifying nightmares) after tetanus.[12] In these human patients, there was no history of abnormal sleep patterns before developing tetanus and the sleep disturbances spontaneously resolved over a period of approximately 1-3 years. It was not noted whether dream enactment was present in these patients, contributing to their frequent waking.

While tetanospasmin toxin is unable to reach the brain via the bloodstream because of its inability to cross the blood-brain barrier,[13] it can reach the brainstem, midbrain, and hypothalamus via retrograde intraneuronal transport.[1] Release of glycine and GABA are prevented, with experimental studies demonstrating disinhibition of cortical neurons after injection of tetanospasmin into the cerebral cortex, lasting for over 1 month.[14,15]

REM sleep is characterized by cortical arousal, pontine-geniculate-occipital waves (stimulating brainstem motor centers during dream activity), and muscle atony. These features are governed by the pedunculopontine nuclei/laterodorsal tegmental nuclei pathways to the thalamus, the pontine reticular formation, and the ventromedial medullary reticular formation.[16] The "midbrain extrapyramidal area" (MEA) has been demonstrated to affect movement in proportion to behavioral state and the retrorubral and subcuneiformis nuclei appear to modulate limbic behaviors.[16] Development of RBD requires the loss of REM atony with concurrent disinhibition of the mesencephalic motor pattern generators.[17] Lai and Siegel experimentally demonstrated in cats that the systems responsible for atonia and locomotion are colocalized in the pons, providing an anatomical explanation for their simultaneous dysregulation during RBD.[18] Therefore, loss of inhibition of glutaminergic and cholinergic neurons in the above areas can result in complex motor behaviors during REM sleep. GABAergic output from the basal nuclei acts to inhibit the glutamatergic retrorubral field and/or MEA neurons that activate the ventromedial medullary zone responsible for maintenance of atonia during REM sleep.[16] It is possible that tetanospasmin binding and its subsequent prevention of GABA release results in loss of this inhibitory basal nuclei output and inappropriate activation of motor centers and failure of muscle atony during REM sleep.

In humans, the International Classification of Sleep Disorders advised that a diagnosis of RBD requires demonstration of the presence of REM sleep without atonia on polysomnography, absence of EEG epileptiform activity during REM sleep, dream enactment behavior and/or abnormal REM sleep behavior documented during

TABLE 3 Reported "dream" activity before developing tetanus for dogs with and without clinically probable RBD after tetanus

	No tendency to dream	Twitching	Running	Vocalization
Dogs with cpRBD (n = 16)	5 (31%)	10 (63%)	5 (31%)	3 (19%)
Dogs without cpRBD (n = 5)	1 (20%)	2 (40%)	2 (40%)	2 (40%)

TABLE 4 Number of sleep behaviors (twitching, running, and/or vocalization) displayed during "dreaming" before developing tetanus in dogs with and without clinically probable RBD

	1 behavior	2 behaviors	3 behaviors
Dogs with cpRBD (n = 11)	6 (55%)	3 (27%)	2 (18%)
Dogs without cpRBD (n = 4)	1 (20%)	3 (75%)	0 (0%)

polysomnographic recording, and the inability to better explain the sleep disorder by another disorder or through medication/substance use.[8] Nocturnal epileptic seizure activity manifesting as dream enactment has been described in people, with EEG activity arising from the REM phase of sleep and the condition proving responsive to administration of AEDs.[17] Although EEG recordings were not available for these dogs, the episodes were considered clinically unlikely to be epileptic seizure activity on the basis that these dogs could be easily woken from the episodes, post-ictal signs were lacking, there were no autonomic signs and, in dogs where these were trialed, there was no response to AEDs. Obstructive sleep apnea-induced REM sleep arousal has also been reported as a cause of immediate dream enactment in humans, after oxygen saturation nadirs of 68%-82%[19] and periods of obstructive apnea lasting up to 51.8 ± 16.5 seconds[20] during REM sleep. While the oxygen saturation level just before onset of the abnormal sleep behaviors was unknown in our cases, in dogs for which video footage or detailed medical records of the episodes witnessed by veterinary staff were available there was no overt ventilatory dysfunction or change in respiratory pattern before the episode onset. Therefore, although a definitive diagnosis of RBD could not be made in these dogs, the abnormal sleep behavior was considered consistent with clinically probable RBD.

Our study was limited by its retrospective nature and the necessity for questionnaire-based information. Inability to obtain post-discharge data for all 50 surviving dogs prevented determination of the prevalence of post-tetanus cpRBD in our study population. It could be argued that a questionnaire format introduces bias toward responses from owners of dogs affected by the condition of interest. However, in our study, questionnaires were not completed by owners of 3 dogs known to have developed cpRBD based on medical records (before discharge or post-discharge based on recorded owner updates) indicating this was not the case. To avoid introducing bias, the known prevalence of post-tetanus cpRBD in our population was not calculated based on the total number of returned questionnaires but on the total number of potential cases.

The retrospective nature of data collection and its reliance on owner memory will have impacted upon the accuracy of owner-reported figures regarding time of onset, time to improvement and even severity of the abnormal dream activity. However, the data obtained is still pertinent in providing owners of future cases with guidelines regarding the potential development and expected course of this condition.

The retrospective nature also prevented utilization of standardized, objective parameters for judgment of clinical severity. The low number of dogs known to have not developed cpRBD post-tetanus was also too low to permit statistical evaluation for determination of significant differences between cpRBD and non-cpRBD dogs and/or risk factors for the development of cpRBD. However, objective measures such as a longer time from identification of a wound/source of infection to development of clinical signs, a longer time from onset of clinical signs to presentation at a referral center and a shorter duration of hospitalization, all possibly suggesting a less severe clinical picture, were noted in dogs that did not develop cpRBD. A more severe clinical picture in cpRBD dogs was also suggested by the observation that the administration of a propofol, medetomidine, and/or magnesium sulfate CRI was only required in dogs that were known to have developed cpRBD or to have died. Furthermore, with the exception of 1 non-cpRBD dog, a midazolam CRI and the requirement for an indwelling urinary catheter were only reported in dogs with cpRBD or that died. No non-cpRBD dogs required a tracheostomy tube. However, in 1 dog with post-tetanus cpRBD clinical signs were confined to the head with no generalization throughout the course of disease. Further data from cases without cpRBD is necessary to statistically determine whether clinical severity, as well as breed and characteristics of pre-tetanus sleep behavior, might be risk factors in the development of post-tetanus cpRBD.

As reported previously, it is often not possible to isolate *C. tetani* from wounds,[21] and obvious wounds/sources of infection might not be evident in all dogs.[3–5] Therefore, the diagnosis of tetanus is typically presumptive, made on the basis of characteristic clinical history, clinical signs, and their progression, exclusion of other causes of tetany and response to treatment. Although a positive clostridial culture was only achieved in 4/12 (33%) cultures of the suspected infection source in our study, this is higher than previous canine studies (0%[5]-20%[4]).

The clinical manifestation of RBD/cpRBD shares many characteristics with epileptic seizure activity, with paddling, twitching, and jaw chomping arising from a state of rest and potentially an apparently nonresponsive mental status during the episode. As epileptic seizures have previously been reported as a consequence of tetanus,[3] without careful questioning of owners/colleagues, attempting to wake the dog or obtaining an EEG recording there is a great potential for misdiagnosis of dogs with post-tetanus cpRBD. Post-tetanus epileptic seizures have been reported to have the potential to spontaneously resolve with recovery from tetanus[3] and in our study cpRBD resolved within 6 months in 44% of dogs. However, 63% of owners in our study considered their dogs' episodes moderate or marked in severity. This, combined with the perceived refractory nature of the episodes with regards to AED administration, does risk potential euthanasia of misdiagnosed dogs. Therefore, owners of dogs affected by tetanus should be counseled that RBD/cpRBD could develop and, to assist in diagnosis, video footage should be obtained, and they should establish whether they can wake their pet, if safe to do so. As a previous study has shown a relatively low level of interobserver agreement regarding classification of paroxysmal events in dogs and cats as epileptic seizures or not on the basis of video footage alone,[22] where possible,

EEG and polysomnography recording should be obtained during an episode in order to reach a definitive diagnosis.

Interestingly, despite 63% of owners in our study considering their dog's cpRBD episodes to be moderate or marked in severity, the dog's quality of life was perceived to be impaired in only 3 dogs (1 minimally so [moderate cpRBD severity] and 2 dogs with a mildly impaired quality of life [moderate and marked cpRBD severity in 1 case each]). Unfortunately, the reasons for the discrepancy in answers were not explored further. However, both dogs considered to have mildly impaired quality of life exhibited cpRBD every time they slept (2/4 dogs with cpRBD every time they slept) and were initially disorientated/confused when waking (2/5 dogs that were not immediately normal on waking). This could suggest that a combination of episode severity, frequency, and behavior on waking could have contributed to the perceived effect of cpRBD on these dogs. Unfortunately the effect of sleep disturbance on daytime activities was not explored in this study, and this might also have been a contributing factor to perceived worsening of quality of life. However, as there was considered to be no effect of cpRBD on the quality of life of 82% of affected dogs, it is likely that the cpRBD episodes did not adversely affect the daytime activities of the majority of dogs in our study.

Onset of cpRBD occurred before discharge in 25% of these cases. Sleep behavior consistent with cpRBD was noted by owners on the first day/night of discharge in 44% of the dogs for whom cpRBD was first reported post-discharge. Despite all dogs being under close supervision during hospitalization (either 24 hour monitoring by a staff member physically present in the dog's immediate vicinity or via a live-feed monitored camera), it is possible that abnormal sleep behaviors could have been missed by staff. Alternatively, as sleep disruption is a commonly recognized consequence of hospitalization and ICU care in humans,[23] this close monitoring might have prevented dogs from reaching an appropriate depth of sleep for an appropriate duration of time to manifest cpRBD during the hospitalization period.

Our study demonstrates abnormal sleep behaviors, consistent with clinically probable RBD, is a common sequel to tetanus in dogs. This condition should be distinguished from epileptic seizure activity in affected dogs. Although considered by more than half of owners to be moderate or marked in their severity, these episodes had no perceived effect on the quality of life in the majority of dogs, with the adverse effect deemed minimal or mild when present. Episodes of cpRBD typically improved in severity, frequency, or both severity and frequency with spontaneous resolution in almost half of affected dogs; therefore, the development of cpRBD should not be considered to be associated with a negative prognosis. Further studies are necessary to establish risk factors for the development of this condition.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The study was approved by the ethics committees of both the Animal Health Trust (20-2016) and the Royal Veterinary College (URN 2016 1624b).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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