VIEWPOINT PIECES

Is there a link between bacteriuria and a reversible encephalopathy in dogs and cats?

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Bacteriuria has been associated with abnormal neurological status in humans, especially geriatric patients. In this report, we review 11 cases (seven dogs and four cats) that support an association between bacteriuria and abnormal neurological status in veterinary medicine. These cases showed diffuse forebrain signs with or without brainstem signs, but primary brain disease was excluded by MRI and cerebrospinal fluid analysis. Bacteriological culture of urine was positive in each animal and neurological deficits improved or resolved with initiation of antibiosis ± fluid therapy and levetiracetam. While further studies are needed to definitively confirm or refute the link between bacteriuria and a reversible encephalopathy, urine bacteriological culture should be considered in veterinary patients presented with acute onset forebrain neuro-anatomical localisation, even in the absence of clinical signs of lower urinary tract inflammation.

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INTRODUCTION

In human medicine, bacteriuria has been associated with a range of neurological deficits, including confusion, delirium, drowsiness, gait disturbances and worsening of pre-existing neurological disorders such as Parkinson's disease and stroke (Manepalli *et al.* 1990, Hufschmidt *et al.* 2010, Eriksson *et al.* 2011). Most commonly affecting the geriatric population, neurological deficits can be severe, with reports of patients presenting stuporous or comatose (de Jonghe *et al.* 2002, Gabra *et al.* 2003, Sato *et al.* 2008). Neurological deficits typically improve on initiation of appropriate antibiotics alongside symptomatic treatment, suggesting a causative link. Despite the growing body of clinical data supporting an association between bacteriuria and neurological dysfunction, definitive evidence of causation remains lacking and the topic continues to be a focus of clinical research and debate (Balogun & Philbrick 2014, Mayne *et al.* 2019).

Delirium has been defined as an acute onset, transient syndrome characterised by global impairment of cognitive function, reduced level of consciousness and altered psychomotor activity (Lipowski 1990). Acute onset or worsening delirium has been associated with bacteriuria in elderly human patients (Levkoff *et al.* 1988, Mccue 1993, Juthani-Mehta *et al.* 2008, Eriksson *et al.* 2010, Mayne *et al.* 2019). A recent systematic review reported that clinical bacteriuria was found in 26–32% of patients with delirium, compared to 13% without delirium. In patients with clinical bacteriuria, 30–35% were found to show signs consistent with delirium, compared to 8% without clinical bacteriuria (Balogun & Philbrick 2014). However, as both delirium and bacteriuria are prevalent in elderly hospitalised patients (Nicolle & Long-Term-Care-Committee 2001, Gau *et al.* 2009, Balogun & Philbrick 2014), it remains possible that the two are unrelated.

Subclinical bacteriuria is defined as bacteria in the urine without associated clinical signs, while in clinical bacteriuria (i.e. urinary tract infection) bacteria in the lower urinary tract result in clinical signs such as pollakiuria, dysuria and/or haematuria (Weese *et al.* 2019). The mechanisms by which bacteriuria (clinical or subclinical) cause neurological deficits are poorly understood, but are suspected to be multifactorial, and may include hyperammonaemia, urine retention and systemic inflammation (Gabra *et al.* 2003, Albersen *et al.* 2007, Sato *et al.* 2008, Cordano *et al.* 2014, Kenzaka *et al.* 2015). Neurological signs associated with bacteriuria are predominantly consistent with forebrain dysfunction, although in more severe cases presenting with stupor, coma or cranial nerve deficits, brainstem involvement is also thought to occur (Kalvas & Monroe 2019).

To our knowledge, there are no veterinary reports documenting an association between bacteriuria and abnormal neurological status in dogs or cats. However, anecdotally, we suspect that this is a clinical scenario encountered in veterinary medicine. In this report, we will review 11 cases (seven dogs and four cats) that suggest a potential association between bacteriuria and abnormal neurological status. The included cases presented with neurological deficits consistent with diffuse forebrain, or forebrain and brainstem, localisation, in which extracranial causes and structural (including inflammatory) brain disease were excluded, but in which urine bacteriological culture was positive, and neurological deficits promptly improved or resolved with initiation of antibiosis and supportive care.

MATERIALS AND METHODS

Digital medical records from January 1, 2000 to March 30, 2017 from the Royal Veterinary College were searched for the following terms: "urinary tract infection," "UTI,", "bacteriuria" and "encephalopathy," "ataxia," "obtundation," "seizure" or "forebrain localisation." Twenty-seven dogs and 11 cats with complete medical records, a history of seizures and/or neurological deficits consistent with a forebrain, or forebrain and brainstem, neuroanatomical localisation, a positive urine bacteriological culture (48 hour aerobic and anaerobic culture of a urine sample collected by cystocentesis) and that had undergone MRI of the brain, as well as cerebrospinal fluid (CSF) analysis, were reviewed. Cases were excluded if clinical records were incomplete or unavailable for review, or if there was evidence of intracranial or concurrent systemic disease, such as hepatic dysfunction or a portosystemic shunt, that could cause or contribute to the presenting neurological signs. The study was approved by the Institute's Ethics and Welfare Committee.

Information retrieved from the medical records included signalment, duration and type of clinical signs, general physical and neurological examination findings, diagnostic test results [including haematology, biochemistry, plasma glucose concentration, plasma ammonia concentration, urinalysis, abdominal ultrasound, CSF analysis (including total nucleated cell count, cytology and total protein concentration) and MRI], treatments administered, duration of hospitalisation and response to treatment. Follow-up information was obtained from daily neurological examinations while hospitalised, neurological status at hospital discharge, re-examination appointments at the referral hospital, as well as from referring veterinary surgeons' clinical records.

CLINICAL CASES: DOGS

Seven dogs (Table 1) with a median age of 10.8 years (range 4.5–15.25 years) presented to the neurology (n = 6) or internal medicine (n = 1) service with a history of acute onset seizures (generalised in two, focal in two, both generalised and focal in one), mentation changes (n = 2), generalised proprioceptive ataxia (n = 1) and abnormal tremor episodes (n = 1). The median duration of presenting signs was 5 days (range 2–14 days). One dog (Case 7) received diazepam and phenobarbital intravenously immediately before referral, and one dog (Case 1) was receiving oral clonazepam. On presentation, neurological examination findings were consistent with diffuse forebrain dysfunction. One dog (Case 6) had clinical signs consistent with urinary tract infection (pollakiuria and dysuria) and two dogs (Case 1, 7) had polyuria, one of which was also polydipsic with urinary incontinence.

The results of the diagnostic investigations are shown in Table 1. All dogs underwent MRI of the head, which was normal in five and showed Chiari-like malformation in one case, and T1-weighted hyperintensity of the lentiform nuclei in one case. This latter dog had a normal bile acid stimulation test result and normal findings on abdominal CT. Cerebellomedullary cistern CSF analysis was normal in all dogs. No dog had plasma ammonia concentrations assessed. Urine sediment examination was performed in five dogs and revealed abundant bacteria (n = 4) and white blood cells (n = 5). Bacteriological culture of a urine sample collected by cystocentesis was positive in all dogs: *Escherichia coli* (n = 3), *Enterococcus faecalis* and *E. coli* (n = 1), *Staphylococcus pseudointermedius* (n = 2) and *Klebsiella spp*. (n = 1).

Pending bacteriological culture results, empirical antibiotic treatment was initiated in five dogs with amoxicillin clavulanate (n = 4) (Clavaseptin, Vetoquinol) or cephalexin (Rilexine, Virbac) (n = 1). Final antibiotic choice was based on the results of culture and sensitivity testing; six dogs received amoxicillin clavulanate and one received trimethoprim-sulfonamide (Tribrissen, Jurox). Six dogs additionally received intravenous fluid therapy (IVFT) from the first day of hospitalisation. One dog (Case 6) was receiving anticonvulsant medication (phenobarbital and potassium bromide) for previously diagnosed idiopathic epilepsy; serum concentrations were found to be within the therapeutic ranges and no alterations were made to the anticonvulsant treatment protocol. Of the four dogs that presented with acute onset seizure activity, and no prior history of seizures, three received levetiracetam from the day of hospital admission, which was continued for a median of 14 days (range 3–14). All cases showed a prompt and sustained improvement of neurological deficits and seizures within 1–3 days of initiating treatment. Antibiotic treatment duration was recorded in six dogs, with a median of 14 days (range 14–28). The median duration of hospitalisation was 2 days (range 1–3 days).

Follow-up information was available for six dogs (median follow-up time of 4.5 months, range 3–8). The dog with previously-diagnosed idiopathic epilepsy showed resolution of the presenting obtundation and focal seizures with antibiosis and IVFT. Of the remaining five dogs, four showed a resolution of neurological deficits, and one showed a marked improvement. No further seizures were observed in the four dogs presenting with new and acute onset seizure activity.

CLINICAL CASES: CATS

Four female neutered cats (median age of 5.5 years (range 2.5–9) presented to the neurology service with an acute onset of mentation changes (n = 3), seizures (n = 3; generalised in two cats and focal in one), inappetance (n = 2) and proprioceptive ataxia affecting all limbs (n = 2) (Table 2). The median duration of

Table 1. Signalment, presentation, diagnostic test results, treatment and outcome of seven dogs with neurological deficits suspected to be secondary to bacteriuria

Case No.	Signalment	Presenting signs	Durations of clinical signs (days)	Presence of clinical signs of urinary tract infection (Y/N)	Treatment received prior to referral	Neurological examination findings	Haematology and biochemistry	Urinalysis	Urine culture	MRI of the head and CSF analysis	Additional diagnostics	Treatment	Time to initial clinical improvement (days)	Duration of hospitalisation (days)	Outcome
1	4.5yo F(N) Husky	Three acute onset generalised seizures. (Last recorded seizure 5 hours prior to presentation)	5	N (Polyuria)	Clonazepam PO	Obtunded, non-ambulatory tetraparetic with proprioceptive ataxia of all limbs, reduced postural reactions in all limbs, reduced menace response bilaterally.	Mild hypocalcaemia	USG 1.015. WBCs 5–20 per hpf.	*Staph. pseudointermedius*	Normal	Normal BAST.	14 days amoxicillin clavulanate. 14 days levetiracetam. IVFT.	1	2	Marked improvement in obtundation, tetraparesis and ataxia with initiation of treatment. No further seizures. Resolution of the polyuria and normal neurological status by 2 days. Normal at 6-month follow-up. Lost to follow up thereafter.
2	10.75yo F(N) Border collie	Three acute onset focal seizures observed over 4 days (Last recorded seizure 1 day prior to presentation).	4	N	None	Mildly delayed postural reactions in pelvic limbs	Mild lymphopaenia	NA	*Klebsiella spp.*	Normal	None	14 days amoxicillin clavulanate. 3 days levetiracetam. IVFT.	2	3	No further seizures and resolution of postural reaction deficits following initiation of treatment. Negative urine culture reported 21 days after discharge. Euthanized 8 months later for unrelated disease.
3	6.25yo M(N) English springer spaniel	Mentation changes and generalised proprioceptive ataxia. Mild dehydration.	7	N	None	Profoundly obtunded, reduced to absent postural reactions in all limbs. Absent menace response bilaterally.	Mild hypoalbuminaemia	USG 1.018. 1+ blood. 20 WBCs per hpf, with bacteria.	*E. coli*	Brain MRI: T1W hyperintense lentiform nuclei. Normal CSF analysis.	Normal BAST. Normal ACTH stimulation test. Normal CT thorax and abdomen	10 days Amoxicillin clavulanate. IVFT.	3	3	Marked improvement in mentation and resolution of postural reaction deficits with treatment. Neurologically normal at 5 month follow up
4	12yo M(N) English bull terrier	One generalised and one focal seizure (3 days prior to presentation). History of hypothyroidism (well controlled with levothyroxine).	4	N	None	Mild obtundation. Delayed postural reactions in the pelvic limbs.	Mild elevation in ALKP	USG 1.015. Trace blood. pH 9. 30–40 WBCs per hpf with bacteria.	*E. coli*	Normal	Abdominal ultrasound: polypoid cystitis.	2 days cephalexin, then changed to 28 days trimethoprim-sulphonamides based on sensitivity. IVFT.	1	3	Improved demeanour and no further seizures during hospitalisation. Owners reported full recovery at 14 days post-discharge, lost to follow up thereafter.
5	11.5yo FN Cavalier King Charles Spaniel	Acute onset of abnormal episodes consisting of head nodding, tremors, swaying and collapse lasting a few seconds, and occurring approximately 15 times per day.	14	N	None	Mild obtundation.	Normal	NA	*Staph pseudointermedius*	Normal	None	14 days amoxicillin clavulanate. 14 days levetiracetam.	1	1	Resolution of obtundation with treatment. Negative urine culture 18 days post discharge. Neurologically normal at follow up 4 months later.

Table 1. Continued

Case No.	Signalment	Presenting signs	Durations of clinical signs (days)	Presence of clinical signs of urinary tract infection (Y/N)	Treatment received prior to referral	Neurological examination findings	Haematology and biochemistry	Urinalysis	Urine culture	MRI of the head and CSF analysis	Additional diagnostics	Treatment	Time to initial clinical improvement (days)	Duration of hospitalisation (days)	Outcome
6	5.5yo M(N) Cavalier King Charles Spaniel	Acute onset of disorientation, progressive obtundation, inappetance, five focal seizures in the 12 hours prior to referral. (Last seizure 5 hours prior to presentation). History of idiopathic epilepsy with generalised seizures every 4–5 weeks, managed with phenobarbital and potassium bromide.	10	Y (Pollakiuria and dysuria)	None	Obtundation, reduced menace response bilaterally. Reduced postural reactions in all limbs.	Mild neutrophilia. Mild hypoalbuminaemia and elevated ALKP.	USG 1.020. 20–30 WBCs per hpf, with abundant bacteria.	*E. coli*	Brain MRI: mild ventriculomegaly and Chiari-like malformation. Normal CSF.	Normal BAST. Normal abdominal ultrasound. Therapeutic serum levels of phenobarbital and potassium bromide.	14 days amoxicillin clavulanate. IVFT.	2	2	Gradual improvement in mentation after initiation of treatment Resolution of pollakiuria and dysuria within 48 hrs. Negative urine culture 14 days after discharge, No further focal seizures and neurologically normal at time of follow up 3 months later. Generalised seizures stable at one every 4–5 weeks.
7	15.25yo F(N) Miniature poodle	Acute onset of 3 generalised seizures. (Last recorded seizure 2 hours prior to presentation).	2	N (Polyuria, polydipsia, urinary incontinence were noted)	IV dose of diazepam and phenobarbital immediately prior to referral.	Obtunded. Reduced postural reactions in all limbs. Absent menace response bilaterally.	Mild elevation in urea, mild hypernatraemia.	USG 1.021. 2+ protein. 2+, blood. Abundant WBCs and bacteria.	*Enterococcus faecalis* and *E. coli*	Normal.	Abdominal ultrasound: mild pyelectasia bilaterally, multiple small renal cortical cysts, bladder polyps.	14 days amoxicillin clavulanate. 14 days levetiracetam. IVFT.	1	2	Marked improvement in mentation, and postural reaction deficits following initiation of treatment, mild improvement in menace responses. No further seizures reported. Euthanized 3 months later for unrelated disease.

yrs = years, F = female, M = male, (N) = neutered, (E) = entire, ACTH adrenocorticotrophic hormone, ALKP alkaline phosphatase, hpf high power field, BAST bile acid stimulation test, IVFT intravenous fluid therapy, NA not assessed, PLR pupillary light reflex, USG urine specific gravity, WBC white blood cell
Plasma ammonia concentration was not assessed in any of the included cases

Table 2. Signalment, presentation, diagnostic test results, treatment and outcome of four cats with neurological deficits suspected to be secondary to bacteriuria

Case No.	Signalment	Presenting signs	Durations of clinical signs (days)	Presence of clinical signs of urinary tract infection (Y/N)	Treatment received prior to referral	Neurological examination findings	Haematology and biochemistry	Plasma ammonia concentration (μmol/l, Reference interval: 0–70)	Urinalysis	Urine culture	MRI of the head and CSF analysis	Additional diagnostics	Treatment	Time to initial clinical improvement (days)	Duration of hospitalisation (days)	Outcome
8	4yo F(N) Maine Coone	Lethargy, inappetance, a single generalised seizure (6 hours prior to presentation)	2	N	IVFT	Mildly compulsive.	Mild elevation of CK and ALT.	NA	USG 1.010 3+ protein 4+ blood WBCs <3 per hpf	*E. coli*	Normal	None	10 days cephalexin. 14 days levetiracetam. VFT.	1	2	Rapid resolution of compulsive behaviour and no further seizures following initiation of treatment. Long term levetiracetam dispensed by RVS but discontinued after 15 months of seizure freedom. No further seizures in subsequent 3 months of available follow up.
9	2.5yo F(N) DSH	Acute onset mentation changes	2	N	None	Obtundation, reduced menace response bilaterally, reduced vestibulo-ocular reflex.	Mild neutrophilia. Mild hypokalaemia, mild elevation of creatinine.	238	USG 1.020. Abundant bacteria and WBCs	*E. coli*	Normal	Abdominal ultrasound: bilateral mild pyelectasia, mildly heterogenous appearance to renal pelvic fat.	12 days amoxicillin clavulanate. IVFT.	1	2	Marked improvement in mentation with treatment, resolution of cranial nerve deficits. RVS reported normal neurological examination 4 weeks after hospital discharge with negative urine culture. Lost to long term follow up.
10	7yo F(N) Maine Coone	Acute onset mentation changes, a single generalised seizure (16hours prior to presentation), generalised proprioceptive ataxia, inappetance.	2	N	None	Obtundation, reduced menace response bilaterally.	Normal	60	NA	*E. coli* and *entero-coccus faecalis*	Normal	Normal abdominal ultrasound.	10 days amoxicillin clavulanate. 7 days levetiracetam. IVFT.	1	2	Resolution of neurological deficits with treatment. Negative urine culture 14 days post discharge. Recurrence of seizures 18months later: phenobarbital initiated.
11	8.75yo F(N) Birman	Acute onset of focal seizures, generalised proprioceptive ataxia, episodic vacant mentation. Inappetance.	14	Y (pollakiuria and dysuria)	IVFT and single dose of diazepam IV	Obtundation, reduced menace response bilaterally, reduced vestibulo-ocular reflex.	Mild neutrophilia. Mild hyperkalaemia, mild elevation of urea.	238	USG 1.022 2+ protein 2+ blood pH 8.5 Abundant WBCs and bacteria	*E. coli*	Normal	Normal abdominal ultrasound.	14 days amoxicillin clavulanate. 14 days levetiracetam. IVFT.	2	6	Marked improvement in obtundation with treatment. Resolution of neurological deficits by time of hospital discharge. Euthanized 5 months later for unrelated disease.

yrs = years, F (N) = female neutered, NA not assessed, CK creatine kinase, hpf high power field, ALT alanine aminotransferase, RVS referring veterinary surgeon, USG urine-specific gravity, WBC white blood cell, IVFT intravenous fluid therapy

clinical signs before presentation was 2 days (range 2–14). Two cats (Cases 8 and 11) received IVFT before referral, and one cat (Case 11) received intravenous diazepam following a seizure. Neurological deficits detected on presentation were consistent with diffuse forebrain dysfunction in two cats and forebrain and brainstem (reduced vestibulo-ocular reflex) neuroanatomical localisation in two cats. One cat (Case 11) was observed to demonstrate pollakiuria and dysuria during hospitalisation.

MRI of the head and analysis of a cerebellomedullary cistern CSF sample were normal in all cats. Three cats had plasma ammonia concentrations measured and values were elevated in two (Cases 9, 11). Bacteriological culture of a urine sample collected by cystocentesis was positive in all cats, with *E. coli* cultured in three, and *E. faecalis* and *E. coli* cultured in the fourth.

Empirical antibiosis with amoxicillin clavulanate was commenced in two cats pending the results of urine culture and sensitivity. In the remaining two cats, antibiosis was commenced [amoxicillin clavulanate (n = 1) and cephalexin (n = 1)] following bacteriological culture and sensitivity results. All cats additionally received IVFT that was initiated on the day of hospital admission. Antibiosis was continued for a median of 12 days (range 10–14). The three cats presenting with seizure activity were additionally treated with levetiracetam (for 7, 14 or 450 days), and no further seizures were documented. All cats showed an improvement of neurological deficits and seizures within 1–2 days of initiation of treatment. The median duration of hospitalisation was 3 days (range 1–6).

Follow-up information was available for three cats (at 5, 18 and 19 months). Of two cats presented with generalised seizures, one (Case 8) made a full recovery and oral levetiracetam was discontinued after 15 months of seizure freedom, no further seizures were reported. The second cat (Case 10) received levetiracetam for 14 days and had no further seizures for 18 months, at which time seizure activity was noted and oral phenobarbital treatment was commenced. The remaining cat for which follow-up was available (Case 11) presented with lethargy and focal seizures, showed a resolution of clinical signs for 5 months, before acute development of weight loss and vomiting, at which time the owners elected for euthanasia without further investigations.

DISCUSSION

Case studies in humans have documented acute onset neurological deficits in patients with subclinical or clinical bacteriuria (Samtoy & Debeukelaer 1980, Manepalli *et al.* 1990, Albersen *et al.* 2007, Hufschmidt *et al.* 2010, Eriksson *et al.* 2011, Balogun & Philbrick 2014, Kenzaka *et al.* 2015). Prompt treatment with appropriate antibiotics and supportive care has been associated with rapid improvements in neurological status (de Jonghe *et al.* 2002, Sato *et al.* 2008, Cordano *et al.* 2014). To the best of our knowledge, the potential association between bacteriuria and abnormal neurological status has not been investigated in veterinary medicine. In this report, we review 11 clinical cases with acute onset neurological deficits that improved promptly on initiation of treatment with antibiosis in combination with IVFT and/or an anticonvulsant (levetiracetam). These cases provide preliminary support for an association between bacteriuria and abnormal neurological status in cats and dogs.

Hyperammonaemia is implicated in the pathogenesis of neurological deficits in patients with bacteriuria. Urease production by bacteria such as *Proteus spp.*, *Nocardia spp. and Staphylococcus aureus* in the urinary tract results in the hydrolysis of urea to ammonia, which is subsequently absorbed into the systemic circulation (Arai *et al.* 1989, Albersen *et al.* 2007). In states of hyperammonaemia, glutamine release from astrocytes is impaired. The osmotic effect of accumulated glutamine results in cytotoxic oedema (Albrecht & Norenberg 2006, Salgado & Cortes 2013). Additional pathological consequences of hyperammonaemia include reduced cerebral blood flow (Rao & Norenberg 2001, Jalan *et al.* 2003, Weissenborn *et al.* 2004) and hyperexcitability of neuronal cell membranes (Basile & Jones 1997, Salgado & Cortes 2013). Plasma ammonia levels were assessed in only three cases (all cats) in this series, with elevated concentrations detected in two (Cases 9, 11). Given this small number of cases, it is not possible to deduce the role of hyperammonaemia in the development of neurological signs in the current population. However, it is of note that only one animal (Case 2) in this study had a urease-positive pathogen (*Klebsiella spp.*) cultured. Human cases are reported with normal plasma ammonia concentrations and/or with infections with non-urease producing bacteria. Thus, other factors are likely to play a role in the development of neurological signs and an area of current research is the role of infection, sepsis and systemic inflammation (Soeno *et al.* 2013, Cordano *et al.* 2014, Kenzaka *et al.* 2015). Cytokine-mediated changes in blood–brain barrier permeability, impaired glutamate uptake by astrocytes and altered expression of γ-aminobutyric acid (GABA) receptors may all contribute to an abnormal neurological status (Shawcross *et al.* 2010, Salgado & Cortes 2013). In the current case series, pyrexia was not documented on presentation, and mild neutrophilia was detected in only three animals, suggesting that systemic inflammation is unlikely to be a major factor in this cohort. This is in agreement with a recent study in which elevated rectal temperature was detected in only two of 33 paraplegic dogs with positive urine culture (Rafatpanah Baigi *et al.* 2017). However, further studies to assess markers of inflammation in blood, CSF and urine would be required to investigate the role of systemic inflammation in the development of neurological deficits.

Clinical bacteriuria affects approximately 14% of dogs during their lifetime (Ling 1984). However, a concurrent and associated abnormal neurological status is likely to be much less common, suggesting that patients presenting with neurological deficits may have underlying predisposing or contributing factors. In humans, geriatric patients are over-represented, with associated risk factors including oestrogen deficiency, urinary retention and urinary incontinence (Mccue 1993, Harrington & Hooton 2000, Molander *et al.* 2000, Foxman 2002, Eriksson *et al.* 2010). The veterinary cases reported here showed a wide age range (4.5–15.25 years in dogs; 2.5–9 years in cats) with no clear predilection for geriatric animals, and only one dog (Case 7) demonstrated

urinary incontinence. Further investigation of predisposing factors is warranted.

A history of pollakiuria and dysuria were documented in only one dog (Case 6) and one cat (Case 11). The remaining cases in the current study were considered to have subclinical bacteriuria. Therefore, an absence of clinical signs of lower urinary tract infection should not exclude bacteriuria as a differential diagnosis for dogs and cats presenting with consistent neurological deficits. Recent guidelines from the International Society for Companion Animal Infectious Diseases advise that there are few indications for culture of urine from animals without lower urinary tract signs (Weese *et al*. 2019). We suggest that one possible indication may be cases with abnormal neurological status in the absence of other structural or functional causes.

Appropriate antibiosis and IVFT is the cornerstone of treatment in human patients and is associated with a rapid improvement of abnormal mental status, typically within 1–3 days (de Jonghe *et al*. 2002, Sato *et al*. 2008, Cordano *et al*. 2014, Kenzaka *et al*. 2015). An equivalent time frame for treatment response was found in the dogs and cats reviewed here. The majority (10 of 11) of cases received IVFT during hospitalisation, which is likely to have contributed to their clinical improvement. Correction of pre-existing dehydration may have improved mental status, and the resultant diuresis would be expected to enhance renal excretion of ammonia/urea and other mediators that may contribute to neurological deficits.

In humans, seizure activity is infrequently reported in association with bacteriuria, with cases largely limited to children presenting with febrile seizures (Mahyar *et al*. 2018). In contrast, the majority of veterinary cases reviewed in this report (four of seven dogs, and three of four cats) presented with a recent onset of seizure activity, with three dogs and three cats receiving levetiracetam. Effective seizure control and resolution of postictal deficits is likely to have contributed to their clinical improvement. Given the limitations of our retrospective data set, we cannot make definitive conclusions that bacteriuria caused seizure activity, but it is interesting to note that all cases in the current report demonstrated a resolution of seizure activity, as well as other concurrent neurological deficits, despite the short-term antibiosis and anticonvulsant medication courses.

The cases presented in this report were collated retrospectively and hence are inevitably limited by their clinical record availability, variation in diagnostic investigations and individual case management decisions. Plasma ammonia was measured in only three of the 11 cases, and future studies are needed to evaluate the role of hyperammonaemia in bacteriuria. While diagnostic investigations in each case excluded major concurrent systemic disease, liver function assays and organic acid assessment for urea cycle disorders were not performed. However, the positive, sustained response to short-term treatment seen in all cases suggests that bacteriuria may play a role in the pathogenesis of the acute onset neurological deficits.

In conclusion, while direct evidence of causation remains lacking, the growing body of clinical data in humans would suggest that bacteriuria (clinical or subclinical) should be considered as a potential cause of acute onset abnormal neurological status. This report describes seven dogs and four cats in which treatment of bacteriuria resulted in sustained resolution of abnormal neurological status. Urinalysis, including bacteriological culture and sensitivity, should be performed in patients presenting with an acute onset of neurological deficits (particularly deficits consistent with a diffuse forebrain localisation), even in the absence of clinical signs of lower urinary tract inflammation. Large-scale, prospective studies with standardised diagnostic investigations are needed to further evaluate the suspected link between bacteriuria and a reversible encephalopathy.

Conflict of Interest

No conflicts of interest have been declared. No financial or other support was used in this study.

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