PAPER

Combined cytosine arabinoside and prednisone therapy for meningoencephalitis of unknown aetiology in 10 dogs

OBJECTIVES: **The differential diagnosis for young to middle-aged dogs with progressive neurological signs, focal or multifocal computed tomography/magnetic resonance imaging lesions, mononuclear cerebrospinal fluid pleocytosis and negative infectious titres includes granulomatous meningoencephalomyelitis, breed-specific meningoencephalitis, infectious meningoencephalitis of unknown origin and central nervous system neoplasia. The terminology *meningoencephalitis of unknown aetiology* may be preferable for cases that lack histopathological diagnoses. The safety and efficacy of a combination of cytosine arabinoside and prednisone protocol is evaluated, in this study, for the treatment of meningoencephalitis of unknown aetiology in 10 dogs.**

METHODS: **Cases were selected based on neuroanatomical localisation, negative regional infectious disease titres, cerebrospinal fluid pleocytosis and brain imaging. Clinical response was gauged through follow-up examinations, owner and referring veterinarian surveys and review of medical records.**

RESULTS: **Partial or complete remission was achieved in all dogs; the median survival time for the 10 dogs was 531 days (range 46 to 1025 days), with five of the 10 dogs alive at the time of writing.**

CLINICAL SIGNIFICANCE: **Prednisone/cytosine arabinoside is a safe empirical therapy for dogs with meningoencephalitis of unknown aetiology; this drug combination may prolong survival time.**

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INTRODUCTION

Current testing for canine meningoencephalomyelitis is non-specific and insensitive; the inciting cause is unknown in up to 66 per cent of cases (Tipold 1995, Chrisman 2001). The differential diagnosis for young to middle-aged dogs with focal or multifocal central nervous system (CNS) signs, cerebrospinal fluid (CSF) mononuclear pleocytosis, focal or multifocal variably contrast-enhancing intramedullary computed tomography (CT)/magnetic resonance imaging lesions and negative infectious disease titres typically includes granulomatous meningoencephalomyelitis (GME), the breed-specific meningoencephalitides (necrotising meningoencephalitis [NME] of pug dogs and Maltese terriers and necrotising leucoencephalitis [NLE] of Yorkshire terriers and other small breeds), neoplasia or infectious meningoencephalitis of unknown origin. Without a histopathological diagnosis, the antemortem diagnosis of dogs with this clinical presentation is typically presumptive. The terminology *meningoencephalitis of unknown aetiology* is proposed to describe dogs with CNS inflammatory disease that lacks a histopathological diagnosis. Empirical and symptomatic therapy (cytosine arabinoside [CA]/prednisone) has been evaluated in 10 cases of so-called meningoencephalitis of unknown aetiology.

The prognosis for long-term remission in proven cases of GME, NME and NLE is considered to be poor (Cordy 1979, Vandevelde and others 1981, Cordy and Holliday 1989, Thomas and Eger 1989, Tipold and others 1993, Stalis and others 1995, Munana 1996). Thomas and Eger (1989) reported that most dogs with GME are euthanased or die within three to six months of initial presentation. Munana and Luttgen (1998) reported 42 dogs with histopathologically confirmed

GME and found that dogs with focal GME had a significantly longer median survival time (114 days) than dogs with disseminated GME (eight days) (Munana and Luttgen 1998). Histopathological confirmation of GME in the 42 cases was obtained at post-mortem, so the poor prognosis in these studies may be biased. Others have reported a greater than one-year survival in dogs with presumptive GME that were treated with aggressive immunosuppression including prednisone and azathioprine (Dewey 2003).

While corticosteroids are the mainstay of immunosuppressive therapy for presumptive GME and the breed-specific meningoencephalitides, response to steroid monotherapy is variable and it is often temporary (Munana and Luttgen 1998, Cuddon and others 2002). Several factors hinder an objective study that evaluates adjunct immunomodulatory treatments for meningoencephalitis of unknown aetiology, including infrequent definitive antemortem diagnoses, challenges to follow-up, ethical considerations of withholding adjunct therapy in blinded, placebo-controlled or steroid monotherapy-controlled prospective studies and a paucity of conclusive data for alternative immunomodulatory protocols (for example lomustine [D. Ruehlmann, personal communication], radiation, azathioprine, procarbazine, leflunomide, ciclosporin and CA) (Gregory and others 1998, Munana and Luttgen 1998, Sturges and others 1998, Ryan and others 2001, Cuddon and others 2002, Nuhsbaum and others 2002, Dewey 2003, Adamo and O'Brien 2004). Limited data for the treatment of meningoencephalitis of unknown aetiology prompted an investigation of empirical and symptomatic treatment with a combination of CA and prednisone.

CA is a synthetic nucleoside analogue, which crosses the blood-brain barrier in dogs, undergoes enzymatic activation, competes for incorporation into nucleic acids and competitively inhibits DNA polymerase in mitotically active cells. CA also causes topoisomerase dysfunction and prevents DNA repair (Scott-Moncrieff and others 1991, Garcia-Carbonero and others 2001, Gmeiner and others 2003). Other effects of CA include: inhibition of ribonucleotide reductase, inhibition of membrane glycoprotein synthesis and the promotion of leukaemic cell differentiation in culture (Griffin and others 1982, Garcia-Carbonero and others 2001).

CA is metabolised via deamination in the liver, plasma, granulocytes and gastrointestinal tract. Side effects in dogs are dose dependent and may include myelosuppression and gastrointestinal upset. CA is an effective chemotherapeutic agent for several neoplastic conditions in both human and veterinary medicine (Ruslander and others 1994). Previously, CA/prednisone treatment has been reported for one case of presumptive GME (Nuhsbaum and others 2002). Here the use of a CA/prednisone protocol is reported (Cuddon and others 2002) in 10 dogs, with the objective of evaluating the safety and efficacy of CA for long-term immunosuppressive management of dogs with meningoencephalitis of unknown aetiology.

MATERIALS AND METHODS

Case histories

The 10 dogs were presented to the Cornell University Hospital for Animals (CUHA Ithaca, New York, USA), evaluated by a veterinary neurologist and were treated with prednisone and CA. Six criteria were evaluated for these cases of meningoencephalitis of unknown aetiology: (1) focal or multifocal neuroanatomical localisation, (2) negative blood and/or CSF infectious disease titres, (3) CSF mononuclear pleocytosis (>25 mononuclear cells/μl), (4) CT scan of the brain consistent with focal or multifocal disease, (5) fundoscopic and neurological examination consistent with optic neuritis (blindness with normal electroretinogram in the absence of imaging evidence of thalamic or cerebral disease) and (6) post-mortem histopathological confirmation of meningoencephalitis. Dogs were included in the study if they fulfilled criteria 1 and 2 and at least one criterion of 3, 4, 5 or 6. All dogs were purebreed dogs from one to 10 years of age (Table 1).

A minimum database for each dog consisted of the following: complete blood count (CBC), serum biochemistry profile and blood serology for infectious encephalitis: *Anaplasma phagocytophilum*, *Ehrlichia canis*, *Toxoplasma gondii*, *Neospora caninum* and *Cryptococcus* (nine dogs). CSF serology for infectious meningoencephalitis (five dogs), thoracic radiographs, brain CT scan (nine dogs) and CSF analysis were performed (Table 1). CSF analysis ranged from normal in several dogs to 6860 nucleated cells/μl (normal <5 cells/μl), with 158 mg/dl of protein (normal <25 mg/dl) in dog 7. None of the dogs had noteworthy travel history outside New York; analysis of CSF or serum antibody titres (Table 1) was prioritised based on agents most common in upstate New York. All serum titres were interpreted to be either negative or consistent with exposure only. Intrathecal antibody production was not suspected in any case: all CSF titres were negative or several dilutions lower than concurrent serum titres. One dog (dog 4) had a positive CSF culture (aerobic) for *Staphylococcus intermedius*, but it was thought to be a contaminant (the CSF in this case was devoid of neutrophils and therefore inconsistent with septic meningoencephalitis). All CT scans of the brain included precontrast and postcontrast evaluation using 2 ml/kg intravenous iohexol 350.

Treatment

Each dog was treated initially with immunosuppressive doses of corticosteroids. At the time of CT/CSF tap, some dogs (cases 4, 5, 6, 7, 9 and 10) received a single immunosuppressive dose of 0·1 to 1·0 mg/kg parenteral dexamethasone sodium phosphate (American Pharmaceutical Partners Inc.) or 10 to 30 mg/kg methylprednisolone sodium succinate (Solumedrol; Pharmacia and Upjohn Co.). At the time of diagnosis, all dogs received 1 to 2 mg/kg prednisone (Roxane Laboratories Inc.) twice a day. About 15 mg/kg clindamycin (clindamycin hydrochloride; Greenstone Ltd.) twice a day and 5 mg/kg doxycycline (doxycycline hyclate; IVAX Pharmaceuticals Inc.) twice a day were given initially, but these were discontinued upon the determination of negative infectious disease titres (typically five to seven days after diagnosis).

Table 1. Summary of signalment, clinical signs and diagnostic evaluation of 10 cases of meningoencephalitis of unknown aetiology

Case	Signalment			Neuroanatomical localisation			CSF analysis						CT findings	Infectious disease titres (negative)
	Age (years)	Breed	Sex	Multifocal	Focal	Ocular	Nucleated cells/RBCs (cells/μl)	Total protein (mg/dl)	Cytology: Lymphocytes	Cytology: Macrophages	Cytology: Neutrophils	Interpretation		
1	6	Chihuahua	FN	X			2/731	13	Very few	None	None	WNL	Multifocal hypodensities in cerebrum and cerebellum; mild, diffuse contrast enhancement	N/A (post-mortem revealed NLE)
2	7	Greyhound	FN			X	2/19	12	N/A	N/A	N/A	WNL	WNL	APs, ECs, TGs and NCs
3	1	Miniature schnauzer	ME	X			27/2	27	90%	Few	Few	Mononuclear inflammation	WNL	ECs, EPs, NRs, TGsc, NCsc and CNs
4	1	Italian Greyhound	ME	X			54/694	694	7%	88%	5%	Mononuclear inflammation	N/A	TGsc, NCsc and CNsc
5	5	Jack Russell terrier	MN		Normal neurological exam		316/9	102	64%	25%	11%	Mononuclear inflammation	WNL	
				X			2/6	36	15%	77%	8%	Mild mixed-cell inflammation	Multifocal, coalescing white matter contrast-enhancing lesions	APc, ECc, TGsc, NCsc and CNsc
				X			6/6	66	60%	34%	6%	Mononuclear inflammation	T2: MF HI in T/P lobes; T1 + C: CE of mass in L T lobe + MF CE of cortical white matter	
6	7	Portuguese water dog	FN	X			149/1	32	60%	40%	Few		Intramedullary, contrast-enhancing mass lesion associated with the left parietal lobe	APs, ECs, TGs, NCs, CNs and RRs
7	5	Cavalier King Charles spaniel	FE			X	6860/0	158	Many (90%)	Few (5%)	Few (2%)	Mononuclear inflammation	WNL	
					Normal neurological exam		11/6	41	50%	50%		Mononuclear inflammation		APs, ECs, TGc, NCc and CNs
8	10	Pomeranian	FN	X			1051/4154	137	Many (87%)	Few (10%)	Few (3%)	Mononuclear inflammation	WNL	APs, EPs, TGs, NCs and CNs
9	2	Yorkshire terrier	MN	X			4/433	16	Few	Very few	Very few	WNL	Enlarged, abnormally shaped left lateral ventricle, multifocal hypoattenuating lesions, no contrast enhancement	APs, ECs and CNs
10	2	Weimaraner	FN	X			46/23	39	Many (90%)	Few (10%)	None	Non-suppurative inflammation	WNL	APsc, TGsc, NCsc and CNsc

CSF Cerebrospinal fluid, CT Computed tomography, RBCs Red blood cells, FN Female neutered, WNL Within normal limits, N/A Not available, NLE necrotising leucoencephalitis, s Serum, c CSF, AP *Anaplasma phagocytophilum*, EC *Ehrlichia canis* immunofluorescent antibody (IFA), TG *Toxoplasma gondii* indirect hemagglutination assay IFA, NC *Neospora caninum* IFA, ME Male entire, EP *Anaplasma platys* IFA, NR *Neorickettsia risticii* IFA, CN *Cryptococcus* agar gel immunodiffusion, MN Male neutered, T2 T2-weighted, MF Multifocal, HI Hyperintensities, T Temporal, P Parietal, T1 T1-weighted, C Contrast, CE Contrast enhancement, L Left RR *Rickettsia rickettsii* IFA, FE female entire

CA treatment was initiated at variable intervals after the prednisone treatment (from zero to 60 days later) as an adjunct immunomodulatory agent so that the dose and side effects of prednisone could be minimised. Each dog received CA (Cytosar; Faulding Pharmaceuticals) at a dose of 50 mg/m^2 subcutaneously (SQ) twice a day for two consecutive days (Cuddon and others 2002). The subcutaneous treatment was diluted with saline (2:1::CA: saline) in order to minimise chemical irritation of the surrounding tissues. Three weeks after the first course, each dog was re-treated with CA at a dose of 50 mg/m^2 SQ twice a day for two consecutive days. Every three weeks for four months, each dog received this treatment protocol (50 mg/m^2 SQ twice a day for two days). The CA treatment interval was lengthened by one week every four months (maximum final interval: every eight weeks); prednisone treatment was tapered gradually over three months.

For the first six months of treatment and then approximately every four months thereafter, a CBC was monitored one week after each CA treatment. In dogs with recurrence of clinical signs, prednisone immunosuppression (1 to 2 mg/kg twice a day initially) was reintroduced for approximately three weeks and tapered whenever possible; the CA treatment interval was shortened permanently to the last effective interval. Some dogs required higher doses of CA, permanent prednisone and/or tertiary immunosuppressive chemotherapies (Table 2).

The clinical response to therapy for each dog was determined through follow-up examinations, telephone conversations with owners and referring veterinarians, review of CUHA medical records for each dog and a survey completed by referring veterinarians.

RESULTS

Partial to complete remission was observed in all dogs upon initiation of corticosteroid and CA treatments. The results are summarised for each dog in Table 2. Median survival for all dogs was 531 days (Kaplan-Meier product limit method) (Dawson and Trapp 2001). According to their owners and referring veterinarians, dogs 6, 7, 8, 9 and 10 are alive with subjectively fair (dog 6), good (dog 7) or excellent (dogs 8, 9 and 10) quality of lives at the time of writing; survival ranges were 564 to 1025 days at the time of writing (see Table 2). The dog with the shortest survival duration (46 days) was the only dog in which post-mortem histopathology (disclosing NLE) became available.

In all dogs, prednisone was initiated immediately following diagnosis and then tapered over several weeks after initiation of CA therapy. In several cases (dogs 1, 2, 3, 4, 5, 6, 7 and 9), prednisone treatment was continued long term due to a subtle recurrence of clinical signs, in an attempt to prevent a complete relapse. In dogs treated long term with prednisone, the dose ranged from 0 to 1·7 mg/kg twice a day depending on individual clinical progression; all cases except dogs 8 and 10 required lifelong adjunct prednisone therapy. Side effects in prednisone-treated dogs included polyphagia, polyuria, polydipsia, mature neutrophilia with lymphopenia and mild liver enzyme elevation in most dogs. In two dogs, tertiary immunosuppressive chemotherapeutics were added to the prednisone/CA regimen (procarbazine in dog 6 and leflunomide in dog 5). Patients 1 and 6 required phenobarbital and/or potassium bromide for persistent, episodic seizure activity. Patient 8 received azathioprine for a history of immune-mediated haemolytic anaemia until CA treatment was established.

Neither neutropenia nor thrombocytopenia was observed in any dog during the treatment regimen. The veterinarians or owners of three dogs in the study reported transient post-treatment lethargy, dysphagia or limb tremors in association with CA/prednisone treatment. Mild hair coat and skin changes (increased shedding or alopecia, mild localised dermatitis in four dogs) and transient to intermittent hindlimb weakness (dogs 6, 9 and 10) were reported during treatment with CA/prednisone. In two cases (dogs 8 and 10), the maintenance treatment regimen consisted of CA monotherapy every eight weeks. In these dogs, CBC and blood chemistries normalised following discontinuation of the prednisone. Of the dogs receiving CA monotherapy, dog 8 has had no discernible side effects; dog 10 had focal epidermal haemorrhages of the pinna and ventrum that resolved spontaneously. Dog 10 also had a single episode of hindlimb weakness that resolved with a single dose of parenteral corticosteroid administered by the dog's local veterinarian. The CA dose was not decreased in any dog due to perceived side effects: CA was administered in doses up to 100 mg/m^2 SQ twice a day every three weeks in refractory cases.

DISCUSSION

Antemortem diagnosis of GME or the breed-specific meningoencephalitides (NME and NLE) often lacks histopathological confirmation. CSF tap and neurological imaging can be misleading and are rarely 100 per cent diagnostic (Plummer and others 1992, Speciale and others 1992, Thomas 1998, 1999). Diagnoses of GME or breed-specific meningoencephalitis typically are presumptive and rely upon clinical signs, CSF, neuroimaging and negative infectious disease titres. The terminology *meningoencephalitis of unknown aetiology* is used for cases in which a histopathological diagnosis has not been obtained.

Meningoencephalitis of unknown aetiology in the dog is commonly attributed to GME. GME is an angiocentric, mixed lymphoid, infiltrative process that predominantly affects the CNS white matter. GME is most likely a non-specific neurotropic response of the canine immune system; multiple aetiologies may be responsible (Srinivasappa and others 1986, Kipar and others 1998, Schatzberg and others 2005).

Three forms of GME have been described based on both morphological and clinical neurological abnormalities: disseminated, focal and ocular. Eight dogs with meningoencephalitis of unknown aetiology in the present study suffered from disseminated disease consistent with either GME or breed-specific meningoencephalitis; two dogs were initially diagnosed with presumptive ocular GME based on neuroanatomical localisation, fundic examination, electroretinogram

Table 2. Clinical response and survival time of 10 dogs treated with CA/prednisone (survival time was measured from date of diagnosis until July 14, 2004)

Case	Dose/frequency range of CA	Prednisone (PO) dose range	Other long-term medications (>two-week duration, PO)	Neurological abnormalities pretreatment	Maximum clinical response	Survival time (days)	Outcome
1	50 mg/m^2 Q three weeks to 65 mg/m^2 Q three weeks	1 mg/kg SID to 1 mg/kg BID	Phenobarbital 0 to 4 mg/kg BID	Compulsive circling R, absent menace OD, bilateral nasal hypalgesia, PRD all four limbs	PR for two months with subsequent regression to seizures	NLE: 46 days	Euthanasia
2	50 mg/m^2 Q three weeks	0·8 mg/kg SID to 1·2 mg/kg BID	None	Mydriasis OU, menace deficits OU, decreased PLR OU, verminous grey retinal lesions OU	PR with normal neurological examination for three months then progression to visual deficits, inappetence	MUE: 130 days	Euthanasia
3	50 mg/m^2 Q three weeks	1·2 mg/kg SID to 1·2 mg/kg BID	None	Dull mentation, head tilt/neck flex/circling L, positional nystagmus, PRD LF/RH, intermittent menace OD	PR for more than six months, with recurrence of neurological signs and development of non-regenerative anaemia, hypoalbuminaemia and cough	MUE: 240 days	Euthanasia
4	50 mg/m^2 Q three weeks to 50 mg/m^2 Q four weeks	0·5 mg/kg SID to 1 mg/kg BID	Fludrocortisone 0·02 mg/kg BID to 0·03 mg/kg BID for Addison's disease	Generalised hyperaesthesia (most severe cervical spinal), absent menace OU	CR for two months with subsequent painful/hypertonic limbs, aggression, ultimately haematemesis and vomiting	MUE: 450 days	Euthanasia
5	50 mg/m^2 Q three weeks to 100 mg/m^2 Q three weeks	0·75 mg/kg SID to 1·5 mg/kg SID	Leflunomide 0 to 1·5 mg/kg SID	History of abnormal behaviour and intermittent tremors, normal neurological examination on presentation	CR for five months before first relapse of clinical signs (partial body/head tremors, abnormal behaviour) which persisted despite increased immunosuppression, progression of disease to include balance loss and PRD R > L, seizures	MUE: 531 days	Euthanasia
6	50 mg/m^2 Q three weeks to 100 mg/m^2 Q three weeks	1·3 mg/kg SID to 1·3 mg/kg BID	Phenobarbital 0·6 mg/kg BID to 1·5 mg/kg BID, KBr 0 to 33 mg/kg SID, procarbazine 0 to 1·8 mg/kg SID	SZ, menace deficits OU, blind	CR for five months before first relapse of clinical signs (visual deficits, occasional SZ) which persisted despite increased immunosuppression, L facial paralysis and hindlimb weakness developed	MUE: 564 days	Alive
7	50 mg/m^2 Q three weeks to 75 mg/m^2 Q three weeks	0·43 mg/kg BID to 1·7 mg/kg BID	Ciclosporin 2 per cent ointment OU for KCS	Dull mentation, absent menace and papillitis OU, PRD all four limbs	Visual, CR with recurrence of clinical signs whenever immunosuppressive treatments were decreased in dose or frequency	MUE: 671 days	Alive
8	50 mg/m^2 Q three weeks to 50 mg/m^2 Q eight weeks	0 to 0·7 mg/kg SID	Initially, azathioprine 1·7 mg/kg EOD for IMHA	Head tilt R, ± nasal hypalgesia L, PRD R	CR for duration of follow-up*	MUE: 950 days	Alive
9	50 mg/m^2 Q three weeks to 50 mg/m^2 Q five weeks	0 to 1·5 mg/kg BID	None	SZ, neck flexion and circling R, ± PRD RF, strabismus OU to R, abnormal mentation	CR for more than one year, initially prednisone was discontinued and CA frequency lengthened to five weeks but ultimately prednisone reinstituted and CA Q three weeks, circled occasionally with some hindlimb weakness	MUE: 976 days	Alive
10	50 mg/m^2 Q three weeks to 50 mg/m^2 Q eight weeks	0 to 0·75 mg/kg SID	None	Vertical nystagmus at rest/all head positions, circling R, ± PRD R	CR for duration of follow-up*	MUE: 1025 days	Alive

*During CA monotherapy

CA Cytosine arabinoside, PO Per os, Q Every, SID Every 24 hours, BID Every 12 hours, R Right, OD Right eye, PRD Postural reaction deficit(s), PR Partial remission ≥50 per cent reduction in severity of clinical signs, NLE Necrotising leucoencephalitis, PLR Pupillary light response, OU Right and left eyes, MUE Meningoencephalitis of unknown aetiology, L Left, LF Left forelimb, RH Right hindlimb, CR Complete remission, normal neurological examination on follow-up examinations, 90 to 100 per cent improvement per owners, SZ Seizure(s), KBr Potassium bromide, KCS Keratoconjunctivitis sicca, EOD Every other day, IMHA Immune-mediated haemolytic anaemia, "±" Equivocal or transient, RF Right forelimb
Minimum/maximum dose and frequency, given diluted 2:1::CA:saline subcutaneously BID for two days

and CNS imaging studies. Of the two dogs affected with ocular disease, one was euthanased 130 days after diagnosis (dog 2) and the other is alive at 671 days after diagnosis (dog 7). It is worthy of note that the diagnostic evaluation of dog 2 could not exclude a tumour involving the optic nerve (Table 1).

Pharmacokinetic studies of the CA regimen used in the current report have not been performed and the response of canine leucocytes to CA has not been quantitatively measured. However, pharmacokinetic studies have shown that 600 mg/m^2 intravenous CA concentrates in the CSF in *normal* dogs (Scott-Moncrieff and others 1991). Furthermore, there is substantial evidence that the pharmacokinetics of CA in CSF and plasma are similar between intravenous/subcutaneous administration and between human beings/dogs (Slevin and others 1983, Scott-Moncrieff and others 1991).

Both the therapeutic and toxic effects of CA are dose dependent: side effects in human beings include myelosuppression and gastrointestinal epithelial injury (Garcia-Carbonero and others 2001). In one study in which dogs received an intravenous bolus of 600 mg/m^2 CA, mild thrombocytopenia was the only toxic effect, noted in half of the dogs, with the nadir at eight to 10 days (Ruslander and others 1994). Neither myelosuppression nor gastrointestinal disturbance was observed in the cases reported here. However, alopaecia, dermatitis or other mild skin changes (dogs 4, 5, 6 and 10) were suspected to be due to CA treatment. Integument changes have not been reported previously in dogs. The only other clinical sign associated with CA/prednisone treatment in multiple dogs was transient to intermittent non-progressive pelvic limb paresis (dogs 6, 9 and 10). At the time of weakness, dogs 6 and 9 were receiving prednisone concurrently, so corticosteroid-induced weakness or myopathy cannot be ruled out (Greene and others 1979, Braund and others 1980). The role of CA in causing pelvic limb weakness is unclear (particularly in case 10), and future dogs should be monitored closely.

Two dogs (3 and 4) in the current study were euthanased as a result of concurrent diseases (see Table 2). Post-mortem was not permitted in these dogs. Overall, the CA/prednisone treatment protocol originally described by Cudden and others (2002) is well tolerated by dogs with meningoencephalitis of unknown aetiology.

The cytotoxic effects of CA, unlike prednisone, are dependent upon both cell cycle (S phase) and rate of DNA synthesis (Garcia-Carbonero and others 2001) and may, therefore, be less effective for treatment of acute, fulminating meningoencephalitis of unknown aetiology. However, when used in combination with prednisone, the use of CA has provided a substantial clinical remission in many cases. Prednisone is recommended to address acute disease, but in several dogs, it was weaned to minimal dosages while maintaining fair (or better) quality of lives. In the two cases in which prednisone therapy was completely discontinued, it might be speculated that continued CA treatments are unnecessary.

In dog 9 (976 days in clinical remission), the dog's local veterinarian attempted to increase the CA treatment interval on several occasions. Upon each attempt, the dog had a relapse in neurological signs, suggesting that CA provides a long-term remission rather than a cure. When clinical signs recurred, they were more refractory to treatment compared with the initial observed response. Relapses therefore should be addressed aggressively. In two dogs, tertiary immunomodulatory drugs were added to the prednisone/CA regimen (procarbazine in dog 6, leflunomide in dog 5) based upon refractory disease in each dog. Considering the severe clinical signs that may be associated with relapses, lengthening the CA inter-treatment interval to longer than two months is not recommended at this time.

The lack of histopathological diagnoses before CA/prednisone treatment of dogs with meningoencephalitis of unknown aetiology hinders the ability to reach definitive conclusions for survival times associated with treating specific meningoencephalitides. The only definitive diagnosis obtained at the time of writing was for dog 1 (NLE). This dog was a Chihuahua that was presented in an obtunded state after several months' history of multifocal neurological signs; therapy provided only partial remission. Post-mortem examination of the brain disclosed a notable absence of active inflammation. The lack of recovery in this case may reflect the advanced stage of NLE upon presentation or relative ineffectiveness of CA for use in breed-specific meningoencephalitides.

A second limitation of the present report is the restricted number of infectious disease titres performed. Infectious meningoencephalitis is uncommon in upstate New York; for practical and financial reasons, most cases were tested only for *A phagocytophilum*, *E canis*, *T gondii*, *N caninum* and *Cryptococcus* (Table 1).

Because optimal patient management was prioritised, a final shortcoming of the current study was occasional deviation from a strict experimental design (Table 2). Recurrence of clinical signs occurred in several dogs either when CA/prednisone doses were decreased (dogs 2 and 3), when CA treatment intervals were increased (dogs 7 and 9), or without any obvious change in the treatment regimen (dogs 1, 4, 5 and 6). This variable response to immunosuppressive therapy may have been due to multiple meningoencephalitis aetiologies or individual variation in immunological status.

Follow-up CT scan and CSF tap should be performed in meningoencephalitis-of-unknown-aetiology patients receiving immunomodulatory therapy whenever allowed. Repeat imaging in dog 5 suggested that CNS inflammation was altered by treatment (Fig 1). However, profound decreases in CSF inflammation were noted during a recurrence of clinical signs in dog 5 and during an asymptomatic re-evaluation of dog 7 (Table 1), suggesting that CSF may not accurately reflect disease progression. Both dogs were receiving treatment with CA and corticosteroids at the time of follow-up CSF evaluation.

All dogs alive at the time of writing (dogs 6, 7, 8, 9 and 10) had a complete clinical remission upon initiation of immunosuppressive therapy. A positive initial clinical response to immunosuppression may suggest a better prognosis. Time from onset of clinical signs to addition of CA treatment ranged from four days to six months. The dogs receiving

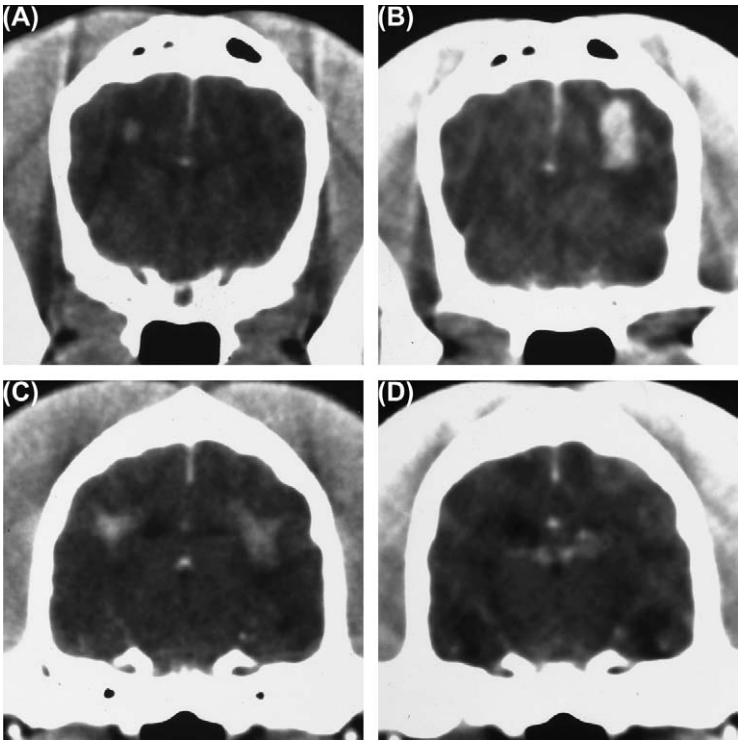

FIG 1. Postcontrast (2 ml/kg iohexol 350) computed tomography scan from two levels of the prosencephalon at seven (A, C) and 14 (B, D) months after initiation of cytosine arabinoside/prednisone. (A) mild contrast enhancement in the right temporal lobe, which resolved seven months later (B). A strong contrast-enhancing lesion was identified in the left temporal lobe (B) that was not identified previously, suggesting progression of disease. (C) multifocal contrast enhancement (temporal-parietal), seemingly confined to the white matter including the left and right internal capsule, centrum semiovale and corona radiata. Seven months later, these contrast-enhancing areas were no longer apparent (D). These results suggest that treatment altered, but did not resolve, the central nervous system inflammatory process in this dog. Despite the addition of leflunomide, dog 5 exhibited intermittent but progressive neurological signs and ultimately was euthanased. Post-mortem examination was declined

CA earliest in their clinical progression did not have the longest survival times, suggesting that CA treatment can be beneficial even when initiated up to 60 days (or longer) after the initiation of prednisone treatment. No other variables measured (for example CSF analysis) were appreciably related to prognosis.

No definitive risk factors for meningoencephalitis were identified in the 10 dogs in the current study. However, three dogs presented with a history of immune-mediated disease (dog 7: keratoconjunctivitis sicca and generalised vaccine reaction, dog 4: juvenile Addison's disease and dog 8: immune-mediated haemolytic anaemia). Antinuclear antibody titres were performed in two of these dogs (dog 7, 1:40; dog 4, 1:20) and were inconsistent with systemic lupus erythematosis (Chabanne and others 1999).

Dogs with meningoencephalitis of unknown aetiology may enter temporary or long-term remission with combination immunosuppressive therapy of prednisone and CA. Therapy should be tailored to the individual patient; the efficacy of this therapy will likely be dependent upon both the individual and the underlying aetiology (i.e. dogs with unidentified infectious encephalitis, neoplastic and breed-specific encephalitides may be less responsive). Until definitive aetiologies can be elucidated and reliable antemortem diagnoses for canine meningoencephalitides can be achieved, these results suggest that empirical therapy with CA (in conjunction with prednisone therapy) is a safe treatment for meningoencephalitis of unknown aetiology that may prolong survival. Future studies should employ histopathology (biopsy or post-mortem) and compare steroid monotherapy with CA/prednisone combination therapy in treating cases of canine meningoencephalitis.

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