Sole prednisolone therapy in canine meningoencephalitis of unknown etiology

Monotherapie met prednisolone bij honden met meningo-encefalitis van onbekende oorsprong

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ABSTRACT

Meningoencephalitis of unknown etiology (MUE) is a frequently diagnosed and often fatal disease in veterinary neurology. The aim of this retrospective study was to assess the efficacy of three different sole prednisolone treatment schedules in dogs diagnosed with MUE. The dogs were diagnosed clinically with MUE based on previously described inclusion criteria, and treated with a three-, eight- or eighteen-week-tapering prednisolone schedule. Thirty eight dogs were included in the study. Seventeen, fifteen and six dogs received the three-, eight- and eighteen-week tapering schedule, respectively. Overall, 37% of the dogs died or were euthanized because of MUE, and a significant difference in survival time was seen between the three treatment schedules. Surprisingly, the highest number of dogs that died because of MUE was seen in the eight-week treatment schedule (56%), followed by the three-week (26%) and eighteen-week (0%) treatment schedule. Based on the results of this study, no definitive conclusions can be drawn regarding the ideal prednisolone dosing protocol for dogs diagnosed with MUE. However, a more aggressive and immunosuppressive treatment protocol might lead to a better outcome.

SAMENVATTING

Meningo-encefalitis van onbekende oorsprong is een vaak gediagnosticeerde neurologische aandoening die meestal fataal afloopt. Het doel van deze retrospectieve studie was het evalueren van drie behandelingsschema's enkel bestaande uit prednisolone, gedoseerd in een afbouwend schema van drie, acht of achttien weken. De diagnose werd gesteld aan de hand van in de literatuur beschreven klinische criteria. Zevenendertig honden werden in de studie opgenomen, waarvan er zeventien, vijftien en zes respectievelijk het gedurende drie-, acht- en achttien-weken afbouwend schema toegediend kregen. Er werd een significant verschil waargenomen in overlevingstijd tussen de drie schema's. Zevenendertig % van de honden in de studie stierf of werd geëuthanaseerd wegens de aandoening. Verrassend genoeg werd de hoogste mortaliteit vastgesteld in de groep die behandeld werd met het acht weken afbouwend schema (56%), gevolgd door het drie weken (26%) en het achttien weken afbouwend schema (0%). Gebaseerd op deze resultaten kunnen er geen definitieve conclusies getrokken worden voor wat betreft het ideale cortisonebehandelingsschema voor honden met meningo-encefalitis van onbekende oorsprong, maar een meer agressief en immunosuppressief schema zou kunnen leiden tot een lagere mortaliteit.

INTRODUCTION

Meningoencephalitis of unknown etiology (MUE) is a group of non-infectious central nervous system diseases with a likely multifactorial pathogenesis (Coates et al., 2014). Making a definitive diagnosis requires histopathological examination of central nervous tissue, but a presumptive antemortem clinical diagnosis can be achieved based on a combination of neurological examination results, magnetic resonance imaging (MRI) findings and cerebrospinal fluid (CSF) abnormalities (Coates et al., 2014). The exact etiology and pathophysiology of MUE are currently unknown, but immunosuppressive drugs are considered to be the cornerstone of the medical treatment of the disease. Several treatment protocols with different associated long-term survival times have been reported, whereby treatment with glucocorticosteroids only is generally associated with shorter survival times (Munana and Luttgen, 1998; Jung et al., 2007; Granger et al., 2010; Flegel et al., 2011) than combination therapy with other immunosuppressive therapies, including cytosine arabinoside, cyclosporine, leflunomide, lomustine, azathioprine, mycophenolate mofetil or radiation therapy (Munana and Luttgen, 1998; Jung et al., 2007; Coates et al., 2007; Granger et al., 2010; Flegel et al., 2011; Beckmann et al., 2015; Barnoon et al., 2016). However, in a clinical setting, adding more expensive immunosuppressive therapies to the glucocorticoid protocol might be financially impossible. In a recently published prospective trial in dogs with MUE, an overall median survival time of 602 days has been reported for dogs receiving immunosuppressive doses of glucocorticosteroids starting at a dose of 1mg/kg twice daily, supporting the use of monotherapy with glucocorticosteroids in the treatment of MUE (Mercier and Barnes Heller, 2015). Therefore, the aims of this study were to retrospectively evaluate the efficacy of three different prednisolone treatment protocols that were historically used (three-, eight- and eighteen-week-tapering schedule) in dogs diagnosed with MUE. In the study, it was assumed that a longer survival time would be achieved with a longer and more immunosuppressive treatment protocol.

MATERIALS AND METHODS

The electronic medical database of Ghent University, Small Animal Department was searched between March 2006 and September 2014. Owner contact was performed in October 2014. Adapted inclusion criteria were used (Granger et al., 2010), considering dogs suitable for inclusion if the following data were available: (1) signalment, (2) localization by neurological examination, (3) inflammatory CSF analysis, (4) intracranial MR and/or CT imaging results, (5) negative infectious disease testing, and (6) long-term follow-up through research of medical records or through telephone contact with the owner or referring veterinarian. Neurological status was recorded at the time of admission and further on a daily basis. The results were recorded daily in a computer program, if the dog was hospitalized. The outcome was defined as successful if dogs were not showing the previously reported neurological signs or if improvement was seen according to the owner or referring veterinarian. An unsuccessful outcome was defined as death or euthanasia because of disease progression or if no change in neurological signs was seen. Relapse was defined as a sudden deterioration of the neurological status after an initial improvement after diagnosis and initiation of treatment. All dogs were only receiving glucocorticosteroids as immunomodulating therapy, and a tapering prednisolone treatment schedule consisting of three, eight or eighteen weeks was used (Table 1). The dogs treated with the three-, eight-, eighteen-week schedule were diagnosed between March 2006 and March 2010, January 2009 and August 2012, and January 2010 and September 2014, respectively. The eighteen-week treatment schedule was started with an immunosuppressive dose of prednisolone, being 3 mg/kg/day, whereas the eight-week schedule was started at an immunosuppressive dose of 2 mg/kg/day. The three-week tapering schedule was started with an anti-inflammatory dose of 1 mg/kg/day. It was recorded whether dogs survived their initial treatment protocol and whether a relapse in neurological signs (sudden deterioration after initial improvement) was seen during treatment together with the associated changes made to the prednisolone schedule. Survival time (ST)

Table 1. Tapering dosing schedules for oral prednisolone treatment.

Three weeks	Eight weeks	Eighteen weeks
1 week 1 mg/kg q24h	2 weeks 1 mg/kg q12h	3 weeks 1.5 mg/kg q12h
1 week 0.5 mg/kg q24h	2 weeks 0.5 mg/kg q12h	6 weeks 1 mg/kg q12h
1 week 0.25 mg/kg q24h	2 weeks 0.5 mg/kg q24h	3 weeks 0.5 mg/kg q12h
	2 weeks 0.25 mg/kg q24h	3 weeks 0.5 mg/kg q24h
		3 weeks 0.25 mg/kg q24h

Table 2. Overview of the most important diagnostic findings in the included cases.

Case number	Breed	TNCC (WBC/µl)	CT	MRI	Description imaging findings	Prednisolone schedule (weeks)	Survival Time (days)
1	American Staffordshire terrier	165	Yes	No	No lesion visible	3	2190
2	American Staffordshire terrier	52.25	No	Yes	No lesion visible	3	1167
3	Boston terrier	24	No	Yes	Disseminated	8	1460
4	Boston terrier	15	No	Yes	Disseminated	8	30
5	Chihuahua	30	No	Yes	Focal forebrain	8	8
6	Chihuahua	9	No	Yes	Disseminated	18	730
7	Chihuahua	16.5	No	Yes	Focal cerebellum	18	70
8	German shepherd	300	No	Yes	Disseminated	8	10
9	Miniature schnauzer	30.25	No	Yes	Focal forebrain / thalamus	8	778
10	French bulldog	22	Yes	No	Disseminated	3	61
11	French bulldog	66	No	Yes	Focal brainstem	8	1275
12	French bulldog	25	No	Yes	Multifocal brainstem and forebrain	18	365
13	Golden retriever	118	Yes	No	No lesion visible	3	370
14	Golden retriever	20	No	Yes	Focal brainstem	3	1095
15	Golden retriever	42.6	No	Yes	Disseminated	18	120
16	Labrador retriever	209	No	Yes	Disseminated	3	1095
17	Labrador retriever	1189	No	Yes	Disseminated	8	150
18	Maltese terrier	74	Yes	No	No lesion visible	3	2190
19	Maltese terrier	66	Yes	No	Disseminated	3	2310
20	Maltese terrier	12.4	Yes	No	Disseminated	3	2035
21	Maltese terrier	800	Yes	No	Disseminated	3	2
22	Maltese terrier	21	No	Yes	Disseminated	8	13
23	Maltese terrier	64	No	Yes	Disseminated	8	84
24	Maltese terrier	96.25	No	Yes	Disseminated	8	180
25	Maltese terrier	120	No	Yes	Disseminated	8	1275
26	Maltese terrier	15	No	Yes	No lesion visible	18	730
27	Maltese terrier	50	No	Yes	Multifocal brainstem and forebrain	18	365
28	Pug	217	Yes	No	Disseminated	3	185
29	Pug	52.25	Yes	No	Disseminated	3	1095
30	Shih tzu	82.5	Yes	Yes	Disseminated	3	1921
31	Shih tzu	55	No	Yes	No lesion visible	8	72
32	Tervueren shepherd	27	No	Yes	Disseminated	8	210
33	Weimaraner	110	No	Yes	Disseminated	8	72
34	West Highland white terrier	33	Yes	No	No lesion visible	3	730
35	West Highland white terrier	500	No	Yes	Disseminated	8	545
36	Yorkshire terrier	33	Yes	No	Disseminated	3	2490
37	Yorkshire terrier	143	Yes	No	Disseminated	3	2490
38	Yorkshire terrier	500	Yes	No	Disseminated	3	6205

TNCC = total nucleated cell count; WBC = white blood cells; CT = computed tomography; MRI = magnetic resonance imaging.

was defined as time from diagnosis to death or euthanasia. A semiparametric cox model (hazard analysis) was fitted to the data to detect differences in survival time between the three treatment groups. All statistic tests were performed using S-Plus. For all analyses, a value of $P < 0.05$ was considered significant.

RESULTS

Thirty-eight dogs met the inclusion criteria. Breeds represented included Maltese terrier (n=10), Yorkshire terrier (n=3), Golden retriever (n=3), Chihuahua (n=3), French bulldog (n=3), Pug (n=2), Labrador retriever (n=2), West Highland white terrier (n=2), Shih tzu (n=2), Boston terrier (n=2), American Staffordshire terrier (n=2) and four other individual breeds. The most commonly presented neurologic signs were abnormal behavior (n=19), altered mentation (n=18) and central vestibular signs (n=19). Brain imaging (CT and/or MRI) was available in all cases. Thirteen dogs (34%) only underwent CT imaging, 24 dogs (63%) only underwent MR imaging and one dog (3%) underwent both CT and MR imaging. No lesion was visible in seven dogs (18%), based on CT (n=4) or MR (n=3) imaging. As required by the inclusion criteria, total nucleated cell count of the CSF was above reference limits (> 5WBC/µl after cisternal collection) in all cases with counts ranging from 9-1189 WBC/µl (median: 55 WBC/µl). An overview of the most important diagnostic findings can be consulted in Table 2.

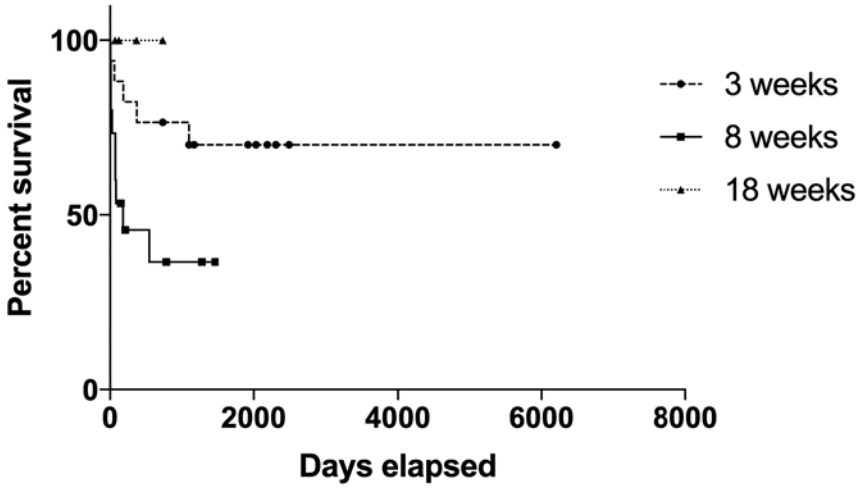

Figure 1. Kaplan-meier survival curve comparing survival times in the three treatment groups. Dogs that were still alive at the time of data capture or died because of unrelated causes, were censored for survival analysis.

Seventeen (45%), 15 (39%), and 6 (16%) dogs received the three-, eight-, and eighteen-weeks prednisolone treatment schedule, respectively. In eight dogs (21%), this therapy was combined with phenobarbital for treatment of seizures. There was a significant difference in ST between the three treatment groups (P=0.028) (Figure 1). Overall, 24 dogs (63%) had a successful outcome, 22 of those dogs were alive at the time of data capture. The remaining two dogs were euthanized because of other reasons 730 and 1167 days after their diagnosis, respectively, and both dogs were not receiving any immunomodulating medication at the time of euthanasia. Fourteen dogs (37%) had an unsuccessful outcome, and died or were euthanized because of MUE. The median survival time (MST) could not be calculated for the group of dogs receiving the three-week and eighteen-week tapering prednisolone schedule, as more than 50% of those dogs were alive at the time of data capture. The MST for the dogs treated with the eight-week tapering schedule, was 180 days. Five dogs died or were euthanized (one in the three-week group en four in the eight-week group) during their treatment schedule. No changes were made to their schedules. Ten dogs (26%) showed a relapse in neurological signs. Four of those dogs did so after terminating their three-week tapering schedule, three dogs after terminating their eight-week treatment schedule, two dogs during their eight-week schedule (after three and six weeks), and one dog after terminating the eighteen-week schedule. If the relapse was seen after termination of the treatment schedule, the same schedule was initiated again (n=7), and the dose was increased again to the starting dose if a relapse was seen before termination of the tapering schedule (n=3). There was no significant difference in relapse rates between the three treatment schedules (P=0.886). An overview of the results can be found in Table 3.

Table 3. Summary of survival, relapse and MST in dogs within the treatment groups.

	Three weeks	Eight weeks	Eighteen weeks
Number of dogs	17	15	6
Dead	5 (2NR)	9	0
Alive	10	6	6
Deceased cases			
During protocol	1	4	0
After protocol	4	5	0
Relapsed cases	4	5	1
During protocol	0	2	1
After protocol	4	3	0
Median survival time	-	180 days	-

NR = not related (dog died for a reason unrelated to MUE)

DISCUSSION

Thirty-eight dogs diagnosed with MUE received oral prednisolone therapy in three different tapering schedules. Overall, 37% of dogs were euthanized because of MUE. The survival curves for the three treatment schedules were significantly different. Surprisingly, the highest mortality rate was seen in the eight-week (immunosuppressive) treatment group (56%), followed by the three-week (anti-inflammatory) (28%) and the eighteen-week (immunosuppressive) treatment (0%) schedule. Possible explanations might be that (1) all dogs at the institution historically received the three-week treatment protocol when a suspicion of non-infectious encephalitis was made. However, as a possibly immune-mediated origin has recently been reported in the literature, dogs diagnosed with MUE admitted with severe neurological signs may have received a longer, more immunosuppressive (eight-week) treatment schedule and (2) the eighteen-week tapering schedule was only introduced in the last four years of inclusion, so the recently included cases in the present study might still have deceased in the following weeks to months, probably having falsely (positively) influenced the results.

In the literature, the MST in dogs diagnosed with MUA and receiving sole prednisolone therapy ranges from 28 - 357 days (Granger et al., 2010), 91 - 329 days (Flegel et al., 2011) and 602 days (Mercier and Barnes Heller, 2015). As more than 50% of the dogs were alive or censored for outcome calculations at the time of data capture, no overall MST could be calculated in the presented study. However, the MST was 180 days in the eight-week treatment group, which appears to be the group with the highest percentage of deceased and relapsed dogs. Further prospective studies should be performed, including more dogs receiving the more immunosuppressive treatment schedules, although comparing immunosuppressive and anti-inflammatory treatment protocols for a presumed immune-mediated disease can cause ethical dilemma.

Pitfalls in the current study are the lack of histopathological confirmation of all cases, the low number of cases and the relatively high percentage of dogs that was diagnosed using CT imaging (34%). However, 18% of the dogs had no visible lesion on CT or MR imaging, which is comparable to the 7% for MRI and 14% for CT described previously (Granger et al., 2010). Prednisolone therapy is associated with common side effects. In order to overcome these effects, other immunosuppressive drugs can be added to the protocol. Looking at the side effects of the prednisolone treatment was beyond the scope of this article, as not all of them were systematically recorded; moreover, these effects are difficult to trace back through telephone contact with the owner or referring veterinarian.

To conclude, the overall prognosis for dogs diagnosed with MUE and treated with sole prednisolone therapy is guarded. Almost 40% of dogs will succumb due to the disease. A long and immunosuppressive treatment schedule is advised, although side effects might be significant.

LITERATURE

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