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1 **Research Paper**

2

3 **Clinical presentation, diagnostic findings and long-term survival in large breed**  
4 **dogs with meningoencephalitis of unknown aetiology.**

5

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26

1 **Abstract**

2

3         Although several studies indicate that meningoencephalitis of unknown  
4 aetiology (MUA) might affect every dog breed at every age, little is known about  
5 clinical presentation, diagnostic findings and long-term survival in large breed dogs.  
6 The aim of this study was therefore to compare the clinical presentation, diagnostic  
7 findings and long-term survival between large and small/medium breed dogs diagnosed  
8 with MUA. One hundred and eleven dogs met the inclusion criteria. Twenty-eight  
9 (25%) dogs were considered large breed dogs, compared to 83 (75%) small/medium  
10 breed dogs. Large breed dogs presented significantly more often with a decreased  
11 mentation. Age, gender, duration of clinical signs prior to diagnosis, presence of  
12 seizures or cluster seizures, variables on complete blood count and cerebrospinal fluid  
13 analysis, and all variables on MRI were not significantly different between  
14 small/medium and large breed dogs. Median survival time was 281 and 106 days for  
15 the large and small/medium breed dogs respectively, with no significant difference in  
16 survival curves for both groups. Although considered not typically affected by MUA,  
17 25% of dogs included in this study were considered large breed dogs. Therefore, MUA  
18 should be included in the differential diagnosis for large breed dogs presenting with  
19 intracranial neurological signs. If diagnosed with MUA, large breed dogs also carried  
20 a guarded prognosis.

21

22 **Keywords**

23         MUO, inflammatory CNS disease, myelitis, encephalitis

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25



## 1 **Introduction**

2           Meningoencephalitis of unknown aetiology (MUA) is a group of idiopathic  
3 non-infectious central nervous system (CNS) diseases, with a likely multifactorial  
4 pathogenesis (Talarico and Schatzberg 2010). The term MUA has been introduced to  
5 encompass all clinically diagnosed cases of non-infectious inflammatory diseases of  
6 the CNS with lacking of histopathological confirmation. More specific, this group  
7 includes encephalopathies such as granulomatous meningoencephalitis (GME),  
8 necrotising meningoencephalitis (NME) and necrotising leucoencephalitis (NLE)  
9 (Zarfoss and others 2006; Talarico and Schatzberg 2010). Middle-aged female toy and  
10 terrier breeds are considered predisposed to develop GME (Munana and Luttgen 1998;  
11 Adamo and others 2007; Talarico and Schatzberg 2010). Necrotising encephalitis  
12 (including NME and NLE) predominantly affects toy and small breed dogs including  
13 Yorkshire Terrier, Maltese Terrier, French Bulldog, Shih Tzu, Lhasa Apso, Chihuahua,  
14 Pug, Pekingese, Papillon, Coton de Tulear and Brussels Griffon (Talarico and  
15 Schatzberg 2010; Cooper and others 2014). Although it is stated that dogs of any breed  
16 and age can be affected by MUA (Coates and Jeffery 2014), literature regarding  
17 differences in clinical presentation, diagnostic findings and long-term survival between  
18 small/medium and large breed dogs is currently unavailable. It is unknown whether the  
19 non-infectious inflammatory encephalopathies diagnosed in large breed dogs are just a  
20 variation on a common etiologic theme or represent a truly different aetiology  
21 compared to the various almost breed-specific encephalitides regularly diagnosed in  
22 small/medium breed dogs. The aims of this study were therefore to describe the  
23 clinical presentation, diagnostic findings and long-term survival in large breed dogs  
24 diagnosed with MUA compared to small/medium breed dogs. We hypothesized that no

1 differences would be detected in clinical presentation, diagnostic findings and long-  
2 term survival between small/medium and large breed dogs diagnosed with MUA.

3

#### 4 **Materials and methods**

##### 5 *Case selection*

6         The electronic medical database of the Small Animal Referral Hospital, Royal  
7 Veterinary College, University of London, was searched between January 2006 and  
8 April 2015 for dogs diagnosed with “MUO”, “MUA”, “GME”, “NME”, “NLE”,  
9 “inflammatory CNS disease”, “non-infectious meningoencephalitis” and the fully  
10 written versions of the above-mentioned abbreviations. Dogs were included based on  
11 the criteria used by Granger and others (2010), if they had (1) complete medical records  
12 available, (2) a complete neurological examination performed leading to a focal or  
13 multifocal intracranial neuroanatomical localisation, (3) inflammatory CSF analysis,  
14 (4) MR imaging of the brain demonstrating single, multiple or diffuse intra-axial  
15 hyperintense lesions on T2W images, and (5) outcome data available through revision  
16 of medical records or contacting the referring veterinarian by email or telephone. Dogs  
17 were excluded if (1) the clinical records or imaging studies were incomplete or not  
18 available for review, (2) dogs were diagnosed with meningomyelitis without clinical  
19 signs of intracranial involvement, (3) no pleocytosis was found on CSF analysis with  
20 the exception of dogs with signs of raised intracranial pressure (ICP) on imaging  
21 studies, in which case CSF collection was not performed, and if (4) outcome data were  
22 unavailable. Dogs with histopathological confirmation of the disease only needed to  
23 fulfil inclusion criteria (1) and (5).

24         Dogs weighing > 15kg were considered large breed dogs, dogs <15kg were  
25 considered small/medium breed dogs. For dog breeds where the body weight varied

1 around 15kg, mean body weight for male and female dogs as reported on the Kennel  
2 Club website ([http://www.thekennelclub.org.uk/services/public/breed/standard-  
3 find.aspx](http://www.thekennelclub.org.uk/services/public/breed/standard-find.aspx)) were used to consider them large or medium/small breed dogs. Information  
4 retrieved from the medical records included breed, age at diagnosis, gender, body  
5 weight, results of general physical and neurological examination and neuroanatomical  
6 localisation, duration of clinical signs prior to diagnosis, results of complete blood  
7 count (CBC) and biochemistry profile, results of CSF analysis, and lactate  
8 concentration on venous blood gas analysis. Duration of clinical signs prior to diagnosis  
9 was classified as peracute (<2 days), acute (2–7 days) or chronic (>7 days). For dogs  
10 that had CSF analysis performed, site of collection (cisternal or lumbar), total nucleated  
11 cell count (TNCC), total protein concentration (TP) and nucleated cell differential count  
12 were recorded. Total nucleated cell count was considered normal if the TNCC < 5  
13 cells/mm<sup>3</sup>. Protein concentration was considered normal for a cisternal collection if <  
14 0,25 g/l and for a lumbar collection if < 0,4 g/l. Possible neuroanatomical localisations  
15 included forebrain, brainstem or cerebellum. Dogs with vestibular signs attributable to  
16 an intracranial lesion were diagnosed with central vestibular signs. If more than 2 of  
17 the above mentioned regions appeared to be affected on the neurological examination,  
18 dogs were given a multifocal neuroanatomical localisation, where dogs with only one  
19 region affected were given a focal neuroanatomical localisation. Magnetic resonance  
20 imaging was performed under general anaesthesia with a permanent 1.5T magnet  
21 (Intera, Philips Medical Systems, Eindhoven, the Netherlands) and all images were  
22 reviewed by a board certified neurologist (SDD) using Osirix DICOM viewer (Osirix  
23 Foundation, V.5.5.2 Geneva, Switzerland). The reviewer was blinded for signalment,  
24 results of the neurological examination and necropsy findings if available. Sequences  
25 could vary, but studies included a minimum of T2-weighted (T2W) (repetition time

1 (ms) (TR)/echo time (ms) (TE), 3000/120), T1-weighted (T1W) (TR/TE, 400/8) and  
2 fluid attenuating inversion recovery (FLAIR) images of the entire brain in a sagittal,  
3 transverse and dorsal plane. The T1W images were acquired before and after IV  
4 administration of paramagnetic contrast medium (0,1 mg/kg, gadoterate meglumine,  
5 Dotarem, Guerbet, Milton Keynes, UK). Variables recorded were lesion localisation  
6 and distribution, presence of parenchymal or meningeal contrast enhancement and  
7 presence of mass effect (brain herniation, midline shift, flattening of gyri/sulci).

8

### 9 *Statistical analysis*

10 Data analysis was performed with the aid of a standard statistical software  
11 package (Prism, Graphpad Software Inc, La Jolla, California, USA). A Mann-Whitney  
12 *U* test was used to compare age, duration of clinical signs prior to diagnosis, venous  
13 blood lactate levels, white blood cell (total, neutrophil and lymphocyte) count on CBC,  
14 TNCC and TP concentration in CSF between small/medium and large breed dogs. A  
15 fisher's exact test was used to compare differences in gender, presence of seizures and  
16 cluster seizures, neuroanatomical localization (mentation, forebrain, brainstem, central  
17 vestibular) and imaging findings (lesion localization, meningeal or parenchymal  
18 contrast enhancement, mass effect, brain herniation, flattening gyri/sulci, rostral or  
19 caudal transtentorial herniation, foramen magnum herniation) between small/medium  
20 and large breed dogs. Numeric variables were expressed as median and IQR. A false  
21 discovery rate (FDR) as used by Benjamini and others (2001) was applied to control  
22 for the increased risk of falsely significant results in the multiple comparisons. Values  
23 of  $P < 0.05$  were considered significant. Survival analysis was performed using both a  
24 Log-rank (Mantel-Cox) and Gehan-Breslow-Wilcoxin test, resulting in median survival  
25 time (MST) calculation and Kaplan-Meier survival curves comparing survival



1 percentage in small/medium and large breed dogs. Survival was defined as time from  
2 diagnosis to death or euthanasia, including whether this happened because of disease  
3 progression or due to unrelated causes, or time from diagnosis to data collection for  
4 dogs that were alive at time of data capture. Dogs that died because of unrelated causes  
5 and dogs that were still alive at time of data capture were censored for calculations.

6

7

## 8 **Results**

### 9 *Signalment*

10 **Database research revealed 549 results. Dogs were excluded if they did not**  
11 **match the inclusion criteria, or if they strictly met the inclusion criteria, but the**  
12 **combination of clinical presentation and imaging findings was more suggestive for**  
13 **another intracranial disorder (neoplasia, vascular lesion) was considered more**  
14 **likely. Finally, 111 dogs were included in this study.** These included 28 (25%) large  
15 breed and 83 (75%) small/medium breed dogs. Large breed dogs represented were  
16 English Springer Spaniel (n=6), cross breed (n=5), Labrador Retriever (n=4), Golden  
17 Retriever (n=2), Akita (n=2), and one each of the following breeds: Border Collie,  
18 Boxer, Bernese Mountain dog, Curly-Coated Retriever, German Wirehaired pointer,  
19 Great Dane, Shar-Pei, Siberian Husky, Welsh Springer Spaniel. Compared to the  
20 general hospital population admitted between January 2006 and April 2015, English  
21 Springer Spaniels were not significantly overrepresented (P=0.196). Small breeds  
22 included West Highland White terrier (n=22), Chihuahua (n=8), Maltese terrier (n=8),  
23 Pug (n=8), French Bulldog (n=7), Cavalier King Charles Spaniel (n=6), crossbreed  
24 (n=6), Yorkshire terrier (n=5), Border terrier (n=2), Boston terrier (n=2), Pomeranian

1 (n=2), Poodle (n=2) and one each of the following breeds: Bichon Frise, Welsh Corgi  
2 Cardigan, Lhasa Apso, Papillon and Sheltie.

3

#### 4 *Clinical presentation and diagnostic findings*

5 Large breed dogs had a significant shorter duration of clinical signs prior to  
6 diagnosis (P=0.012), more often presented with decreased mentation (<0.0001) and less  
7 often with cranial nerve deficits (P=0.027), and were more often diagnosed with a  
8 brainstem lesion on MRI (P=0.039) compared to small/medium breed dogs. However,  
9 when a FDR of 10% was applied, only decreased mentation was found to be  
10 significantly different between both groups (**table 1**). Gender, age at presentation,  
11 neuroanatomical localisation, presence of seizures and cluster seizures, lactate  
12 concentration on venous blood gas analysis, TNCC and TP concentration on CSF  
13 analysis and the remaining MRI findings (meningeal or parenchymal contrast  
14 enhancement, mass effect, brain herniation, flattening gyri/sulci, rostral or caudal  
15 transtentorial herniation, foramen magnum herniation) were not different between  
16 small/medium and large breed dogs. All statistical results can be consulted in **table 1**,  
17 **a clinical summery regarding the large breed dogs can be consulted in table 2.**

18 Serological testing and/or polymerase chain reaction (PCR) for Canine  
19 Distemper virus, *Toxoplasma gondii* and *Neospora caninum* was performed in 19  
20 (68%) large breed dogs and in 59 (71%) small/medium breed dogs. Of the 9 large breed  
21 dogs that did not undergo infectious disease testing, 1 dog had complete necropsy  
22 performed and 4 dogs were still alive at time of data capture with survival times ranging  
23 from 184 – 2039 days. These 4 dogs were all treated with an immunosuppressive  
24 treatment protocol. The 4 remaining large breed dogs died within 20 days after

1 diagnosis and breeds included English Springer Spaniel, crossbreed, Siberian Husky  
2 and Akita.

3 Post-mortem examination was performed in 14 dogs, 8 small/medium breed and  
4 6 large breed dogs. Results included GME (5 small/medium breed, 4 large breed), NME  
5 (3 small breed, 1 large breed) and NLE (1 large breed dog).

6

### 7 *Outcome*

8 All 111 dogs were initiated on immunosuppressive doses of  
9 glucocorticosteroids at time of diagnosis, combined with cytosine arabinoside in 66  
10 (80%) small/medium breed dogs and 18 (64%) large breed dogs. Most dogs on cytosine  
11 arabinoside therapy had regular (3-4 weekly) re-examinations at a dedicated cytosine  
12 arabinoside clinic. Overall, dogs that were alive at time of data capture, were dogs that  
13 received sole prednisolone therapy or combined prednisolone and cytosine arabinoside  
14 treatment.

15 At time of data capture, 11 (39%) large breed dogs and 27 (33%) small/medium  
16 breed dogs were alive. Conversely, 17 (61%) large breed and 56 (67%) small/medium  
17 breed dogs had died. Of the deceased dogs, 15 (88%) large breed dogs and 47 (84%)  
18 small/medium breed dogs died or were euthanized because of disease progression,  
19 compared to 2 (12%) large breed dogs and 9 (16%) small/medium breed dogs that died  
20 or were euthanized for unrelated causes. Overall, 54% of the large breed dogs and 57%  
21 of the small/medium breed dogs died or were euthanized because of disease  
22 progression. The MST was 281 days and 106 days for the small/medium and large  
23 breed dogs respectively. There was no significant difference in survival curves between  
24 small/medium and large breed dogs ( $P=0.664$ ) (**Figure 1**).

25

1 **Discussion**

2           This study evaluated the differences in clinical presentation, diagnostic findings  
3 and long-term survival between small/medium and large breed dogs diagnosed with  
4 MUA. Large breed dogs were found to present significantly more often with a  
5 decreased mentation. No significant difference was seen in survival curves between  
6 small/medium and large breed dogs. To the best of our knowledge, this is the first study  
7 describing clinical, diagnostic and outcome data in large breed dogs with MUA.  
8 Meningoencephalitis of unknown aetiology is generally considered a syndrome  
9 affecting small, toy and terrier breed dogs aged between approximately 3 and 7 years  
10 (Munana and Luttgen 1998; Adamo and others 2007; Talarico and Schatzberg 2009;  
11 Coates and Jeffery 2014). However, a total of 47 large breed dogs are present in the  
12 literature from 1998 to 2015. The distribution of the breeds in our study appears to be  
13 similar. Although the English Springer Spaniel was the most common large dog breed  
14 in our study, it was not significantly overrepresented compared to the general hospital  
15 population. The higher number of this breed in our study therefore likely reflects its  
16 popularity in the United Kingdom. MUA occurred, as expected, more often in  
17 small/medium breed dogs, but still a quarter of dogs in the presented study were large  
18 breed dogs. Ignoring this population of dogs would underestimate the prevalence of  
19 MUA in the overall canine population. Therefore, MUA should be considered as a  
20 differential diagnosis in dogs other than small or toy breeds that have signs suggestive  
21 of inflammatory brain disease.

22

23           Large breed dogs were more likely to present with a decreased mentation  
24 compared to their small/medium breed counterparts. Abnormal mentation in dogs can  
25 be caused by lesions in the forebrain (telencephalon and diencephalon) and/or

1 brainstem (mesencephalon, metencephalon, myelencephalon) (Garosi 2013). A lesion  
2 in the brainstem is considered a typical MRI finding in cases of GME and NLE, but is  
3 considered an uncommon finding in dogs with NME (Coates and Jeffery 2014).  
4 However, histopathological lesions have been identified in the brainstem of Chihuahua  
5 and Pug dogs with NME (Higgins and others 2008; Park and others 2012). In the  
6 presented study, both small/medium and large breed dogs were histopathologically  
7 diagnosed with GME and NME, and 1 large breed dogs was diagnosed with NLE,  
8 which has not yet been previously described. In literature, NLE is mainly affecting  
9 Yorkshire terriers, Maltese Terriers and a French Bulldog (Schatzberg 2005;  
10 Higginbotham and others 2007; Timmann and others 2007; Spitzbarth and others  
11 2010), which are all considered small/medium breed dogs in this study. Necrotising  
12 meningoencephalitis has only been once previously described in large breed dog; a  
13 26kg Staffordshire Bull Terrier mix (Estey and others 2014).

14

15         A limitation of the current study is the lack of histopathological confirmation in  
16 the majority of cases, which makes inclusion of other diseases than MUA possible  
17 (mainly cerebrovascular or neoplastic disease). Based on intracranial MRI, seven  
18 imaging abnormalities have been associated with neoplastic brain disease in one study  
19 (Cherubini and others 2005). These included the presence of a single lesion, regular  
20 lesion shape, presence of mass effect, dural contact, dural tail sign, lesions affecting  
21 adjacent bone and contrast enhancement (Cherubini and others 2005). Another study  
22 demonstrated MRI to be 94.4% sensitive and 95.5% specific for detection of a brain  
23 lesion and for classifying neoplastic and inflammatory disease correctly, but was only  
24 38.9% sensitive for classifying cerebrovascular disease (Wolff and others 2012). For  
25 the presented study, 6 large breed dogs had a focal lesion on MRI of the brain, where

1 inflammatory lesions are more typically associated with multifocal or diffuse lesions  
2 on intracranial imaging (Cherubini and others 2006). Two of those lesions were  
3 histopathologically confirmed as GME or NME. Of the 4 remaining dogs, one dog  
4 (Siberian husky) had a focal lesion in the frontal lobe that showed presence of mass  
5 effect, parenchymal contrast enhancement and dural contact. Although abnormalities  
6 on CSF-analysis do not exclude neoplastic or vascular disease (REF), this dog had an  
7 increased TNCC (35 WBC/mm<sup>3</sup>) and TP concentration (0.35 g/l) on cisternal CSF  
8 analysis. The dog was only 30 months old, and died acutely at home 18 days after  
9 diagnosis after initial improvement on immunosuppressive therapy. The second, third  
10 and fourth dog (2 cross breeds and an English Springer Spaniel) were 26 – 85 months  
11 old at time of diagnosis and had a focal lesion in the piriform lobe (crossbreed) or  
12 brainstem (cross breed an English Springer Spaniel). All three dogs had increased  
13 TNCC and TP concentrations on cisternal CSF analysis, and all were alive 1095 – 1580  
14 days after diagnosis. All dogs had an acute onset of neurological signs, which might  
15 still be compatible with cerebrovascular disease, which might be supported by the long  
16 survival without treatment of those dogs. However, in cerebrovascular disease, contrast  
17 enhancement should only be visible after 7-10 days in dogs with ischaemic infarcts,  
18 and after 6 days to 6 weeks in dogs with haemorrhagic infarcts (Garosi 2012). All dogs  
19 with a focal lesion had intracranial imaging within 5 days after onset of neurological  
20 signs, and all lesions showed parenchymal contrast enhancement, which was  
21 considered less typical for cerebrovascular disease. Neoplastic disease can however not  
22 be excluded in those cases, although all 4 dogs were still young at time of diagnosis (2-  
23 5y of age) where brain tumors are typically affecting middle-aged to older (over 5  
24 years) dogs and cats, with the majority being greater than 9 years of age (**Dickinson**  
25 **2014; Snyder and others 2006**).

1 Infectious disease testing was lacking in approximately 30% of both  
2 small/medium and large breed dogs. The 9 large breed dogs that were not tested had  
3 focal (n=2), multifocal (n=5) or diffuse forebrain (n=2) lesions on MR imaging.  
4 Necrotising cerebellitis and cerebellar atrophy (Garosi and others 2010) as well as  
5 multifocal brain involvement (Parzefall and others 2014) have been described in  
6 association with *Neospora caninum* infection in dogs. In the study of Parzefall and  
7 others (2014), mild cerebellar atrophy was additionally seen in 3 of 4 dogs. In the  
8 presented study, 11 large breed dogs died within 20 days after diagnosis and after  
9 immunosuppressive treatment. Necropsy confirming GME, NLE or NME was  
10 performed in 6/11 dogs. Of the 5 remaining dogs, all but 1 (Siberian Husky) had  
11 multifocal or diffuse forebrain lesions without cerebellar involvement, and showed no  
12 signs of perilesional edema on FLAIR images as described by Parzefall and others  
13 (2014). Magnetic resonance imaging features of *Toxoplasma gondii* encephalitis have  
14 not yet been described for dogs, but it is known to cause focal granuloma formation  
15 both in the forebrain (Pfohl and others 2005; Falzone and others 2008) and the spinal  
16 cord (Alves and others 2011) of cats. The 4 dogs with multifocal or diffuse brain lesions  
17 all had an increased TNCC with a mononuclear pleocytosis but without signs of  
18 presence of lymphoblastic cells. No further diagnostic investigations for lymphoma  
19 were performed. Gliomatosis cerebri is a central nervous system neoplasia that is  
20 mainly affecting brachycephalic breeds (Boxer, Boston Terrier, English Bulldog, Bull  
21 Mastiff) and MRI mainly reveals single lesions in thalamus and/or brainstem, although  
22 the cerebrum can be involved and sometimes no lesions are visible (Bentley and others  
23 2014). This differential diagnosis seems less likely in these 4 dogs because of their  
24 breeds and the presence of multifocal or diffuse lesions, but necropsy confirmation is  
25 lacking in those cases. Overall, pitfalls of this study are its retrospective character, the

1 lack of histopathological confirmation and infectious disease testing in a number of  
2 cases. In contrary, MUA is considered a clinical and imaging diagnosis in cases were  
3 definitive brain histology is lacking.

4

## 5 **Conclusions**

6 Twenty-five per cent of dogs diagnosed with MUA in this study were  
7 considered large breed dogs. Ignoring this population of dogs would underestimate the  
8 prevalence of MUA in the overall canine population. Large breed dogs presented  
9 significantly more often with a decreased mentation compared to small/medium breed  
10 dogs. The MST was not significantly different between small/medium and large breed  
11 dogs, 281 and 106 days respectively, leading to a guarded prognosis for all dogs  
12 diagnosed with MUA and receiving immunosuppressive treatment. In conclusion,  
13 MUA should be considered as a differential diagnosis in dogs other than small or toy  
14 breeds that have signs suggestive of inflammatory brain disease.

15

16

17



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- 22

1 **Tables**

2

3 **Table 1**

<b>Variable</b>	<b>Small/medium breed dogs (n=83)</b>	<b>Large breed dogs (n=28)</b>	<b>P value/FDR</b>
Signalment			
Age (months)	52 (6 – 146)	60 (10 – 120)	0.7373/0.0678
Male	44 (53%)	17 (61%)	0.0653/0.0143
Female	39 (47%)	11 (39%)	0.0653/0.0178
Duration of clinical signs prior to diagnosis (days)	8 (1-180)	5 (1 – 60)	0.0116/0.0071
Clinical signs			
Seizures	19 (23%)	10 (36%)	0.2164/0.0286
Cluster seizures	13 (16%)	7 (25%)	1.0000/0.0929
Neuroanatomical localisation			
Forebrain	58 (70%)	22 (79%)	0.4875/0.0464
Brainstem	53 (64%)	18 (64%)	1.0000/0.0964
Central vestibular	27 (33%)	4 (14%)	0.0904/0.0214
Abnormal mentation	26 (31%)	25 (89%)	<0.0001/0.0036*
Bloodwork			
White blood cells ( $\cdot 10^9/l$ )	10.6 (3.52 – 32.8)	9.8 (4.66 – 25.1)	0.5888/0.05
Neutrophils ( $\cdot 10^9/l$ )	7.5 (2.4 – 28.3)	7.1 (3.2 – 22.3)	0.4420/0.0429
Lymphocytes ( $\cdot 10^9/l$ )	1.3 (0.1 – 3.6)	1.2 (0.3 – 2.7)	0.3434/0.0393
Venous blood gas			
Lactate (mmol/l)	1.5 (0.6 – 3.6)	1.6 (0.4 – 10.4)	0.8711/0.0786
CSF analysis			

TNCC (WBC/mm <sup>3</sup> )	97 (1 – 2560)	48 (1 – 2220)	0.3360/0.03572
Total protein (g/l)	0.54 (0.11 – 3.51)	0.43 (0.1 – 8.47)	0.7872/0.0714
MRI findings			
Focal lesion	24 (29%)	7 (25%)	0.7163/0.0607
Multifocal lesion	57 (69%)	20 (71%)	0.7335/0.0643
Diffuse lesion	6 (7%)	2 (7%)	1.0000/0.1
Forebrain localisation	66 (80%)	23 (82%)	0.7035/0.0571
Brainstem localisation	41 (49%)	20 (71%)	0.0414/0.0107
Cerebellar localisation	16 (19%)	5 (18%)	0.8893/0.0821
Mass effect	53 (64%)	13 (46%)	0.1297/0.025
Brain herniation	34 (41%)	10 (36%)	0.6586/0.0536
Caudal transtentorial herniation	29 (35%)	10 (36%)	0.9097/0.0857
Foramen magnum herniation	23 (28%)	7 (25%)	0.8066/0.075
Midline shift	31 (37%)	7 (25%)	0.2534/0.321
Flattening gyri/sulci	38 (46%)	13 (46%)	0.9140/0.0893

1

2 Table 1: Investigated variables in small/medium and large breed dogs diagnosed with  
3 MUA. Values are numbers with their percentage, or a median with interquartile range  
4 between brackets. FDR: false discovery rate. \* = P-value below the FDR threshold and  
5 thus considered to be significant.

6

7 Table 2

<b>Breed</b>	<b>Age at presentation (months)</b>	<b>Duration clinical signs prior to presentation (#d)</b>	<b>Serology or PCR on CSF performed</b>	<b>TNC (WB C/m<sup>3</sup>)</b>	<b>TP (g/l)</b>	<b>MRI findings (lesion localisation)</b>	<b>ST (days)</b>	<b>PM diagnosis</b>
<b>Akita</b>	<b>36</b>	<b>2</b>	<b>yes</b>	<b>2220</b>	<b>4,65</b>	<b>Multifocal lesions brainstem and spinal cord</b>	<b>2</b>	<b>NP</b>
<b>Bernese Mountain Dog</b>	<b>45</b>	<b>21</b>	<b>yes</b>	<b>12</b>	<b>0,38</b>	<b>Multifocal lesions forebrain and brainstem</b>	<b>120</b>	<b>NP</b>
<b>Border Collie</b>	<b>70</b>	<b>7</b>	<b>yes</b>	<b>300</b>	<b>2,47</b>	<b>Multifocal lesions forebrain and cerebellum</b>	<b>92</b>	<b>ALIVE</b>
<b>Boxer</b>	<b>68</b>	<b>60</b>	<b>no</b>	<b>NP</b>	<b>NP</b>	<b>Multifocal lesions forebrain, brainstem and cerebellum</b>	<b>1</b>	<b>GM E</b>
<b>Cross Breed</b>	<b>85</b>	<b>5</b>	<b>no</b>	<b>23</b>	<b>0,26</b>	<b>Focal lesion forebrain</b>	<b>1580</b>	<b>ALIVE</b>
<b>Cross Breed</b>	<b>64</b>	<b>30</b>	<b>no</b>	<b>1255</b>	<b>1,31</b>	<b>Multifocal lesions forebrain, brainstem and spinal cord</b>	<b>5</b>	<b>NP</b>
<b>Cross Breed</b>	<b>23</b>	<b>3</b>	<b>yes</b>	<b>555</b>	<b>1,92</b>	<b>Focal lesion brainstem</b>	<b>1</b>	<b>GM E</b>
<b>Cross Breed</b>	<b>26</b>	<b>4</b>	<b>yes</b>	<b>1090</b>	<b>8,47</b>	<b>Focal lesion brainstem</b>	<b>1095</b>	<b>ALIVE</b>
<b>Cross Breed</b>	<b>12</b>	<b>5</b>	<b>yes</b>	<b>90</b>	<b>0,62</b>	<b>Multifocal lesions forebrain, brainstem and cerebellum</b>	<b>2708</b>	<b>ALIVE</b>
<b>Curly-Coated Retriever</b>	<b>63</b>	<b>38</b>	<b>yes</b>	<b>80</b>	<b>0,78</b>	<b>Multifocal lesions forebrain, brainstem and cerebellum</b>	<b>2190</b>	<b>ALIVE</b>
<b>English Springer Spaniel</b>	<b>61</b>	<b>5</b>	<b>yes</b>	<b>62</b>	<b>0,6</b>	<b>Multifocal lesions forebrain and brainstem</b>	<b>2950</b>	<b>ALIVE</b>
<b>English Springer Spaniel</b>	<b>60</b>	<b>2</b>	<b>no</b>	<b>17</b>	<b>0,75</b>	<b>Diffuse lesions forebrain</b>	<b>1</b>	<b>NP</b>



English Springer Spaniel	47	1	yes	12	0,16	Multifocal brainstem lesions	72	AL IV E
English Springer Spaniel	61	5	no	29	0,23	Multifocal forebrain and brainstem lesions	20 39	AL IV E
English Springer Spaniel	39	1	yes	173	0,68	Focal brainstem lesion	11 87	AL IV E
English Springer Spaniel	78	2	yes	NP	NP	Multifocal forebrain, brainstem and cerebellum lesions	70 0	AL IV E
German Wirehaired Pointer	10	4	yes	12	0,23	Multifocal forebrain and brainstem lesions	97 5	AL IV E
Golden Retriever	75	7	yes	1	0,21	Multifocal forebrain and brainstem lesions	1	G M E
Golden Retriever	60	7	yes	22	0,46	Multifocal forebrain and brainstem lesions	18 56	AL IV E
Great Dane	60	2	yes	40	0,1	Multifocal forebrain lesions	1	NP
Japanese Akita	20	2	no	51	0,41	Multifocal forebrain and brainstem lesions	1	NP
Labrador	120	13	yes	8	0,1	Focal lesion forebrain	3	N M E
Labrador	47	7	yes	3	0,24	Multifocal forebrain and brainstem lesions	1	NL E
Labrador	27	7	no	NP	NP	Diffuse forebrain lesions	18 4	AL IV E
Labrador	94	3	no	30	0,43	Multifocal forebrain and brainstem lesions	73 0	AL IV E
Shar-Pei	36	9	yes	NP	NP	Multifocal forebrain lesions	21 29	AL IV E
Siberian Husky	30	2	no	68	0,35	Focal lesion forebrain	18	NP
Welsh Springer Spaniel	89	21	yes	675	5,56	Multifocal forebrain and brainstem lesions	3	G M E

1 **Table 2: Overview of breed, age, duration of clinical signs prior to diagnosis,**  
2 **infectious disease testing results, TNCC in CSF, TP concentration in CSF, MRI**  
3 **findings, ST and post mortem (PM) necropsy findings for the large breed dogs**  
4 **included in this study. NP: not performed.**

5

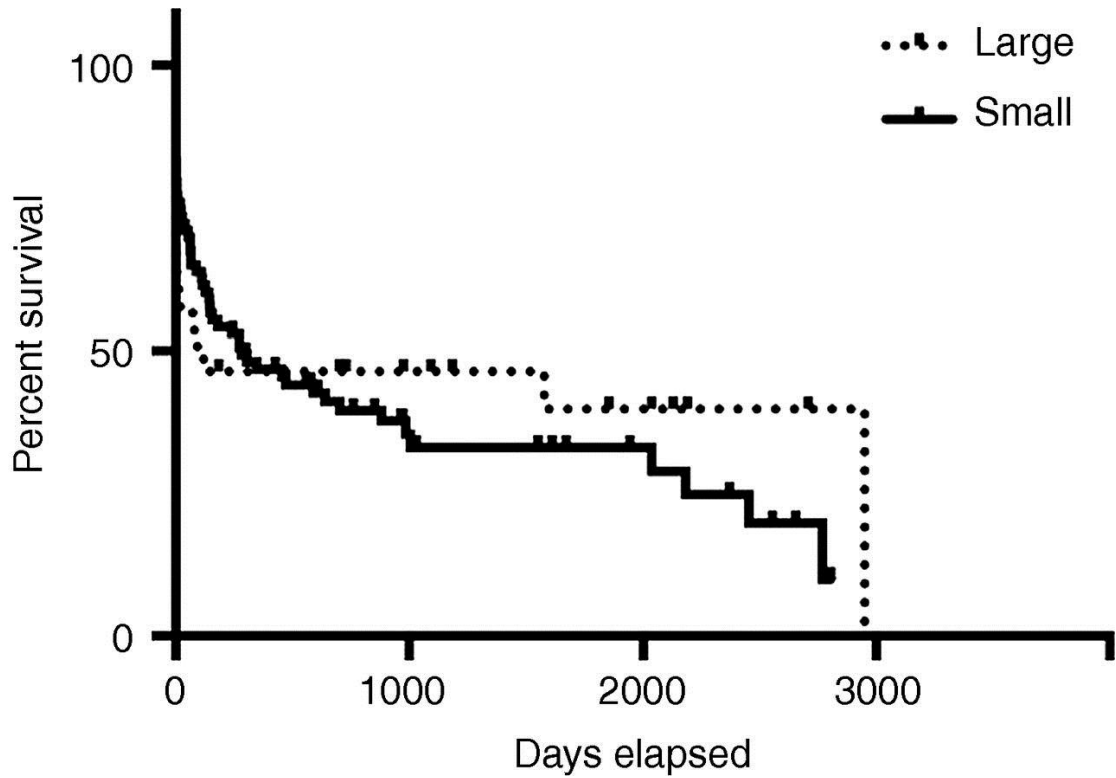
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7

1 **Figure legends**

2

3 **Figure 1**



4

5 Figure 1: Kaplan-Meier survival curve comparing the percentage of survival in  
6 small/medium (full black line) and large (dotted line) breed dogs. Results were  
7 censored for dogs that were still alive at time of data capture (single little blocks).

8