Research Paper

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

Authors

- Ine Cornelis, DVM, DECVN
- Holger A. Volk, DVM, PhD, DECVN
- Steven De Decker, DVM, PhD, MvetMed, DECVN

Personal affiliations

Clinical Science and Services, The Royal Veterinary College, University of London, Hatfield, United Kingdom.

I. Cornelis' current address is Department of Medicine and Clinical Biology of Small Animals, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium

Corresponding author.

Ine Cornelis, Department of Medicine and Clinical Biology of Small Animals, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium.

Telephone: 0032 9 264 77 00

Email address: ine.cornelis@ugent.be (I. Cornelis)

Abstract

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

Keywords

MUO, inflammatory CNS disease, myelitis, encephalitis

Introduction

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

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

Materials and methods

Case selection

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

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

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

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

Statistical analysis

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

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

Results

Signalment

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

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

Clinical presentation and diagnostic findings

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

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

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

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

Outcome

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

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

Discussion

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

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

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

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

inflammatory lesions are more typically associated with multifocal or diffuse lesions on intracranial imaging (Cherubini and others 2006). Two of those lesions were histopathologically confirmed as GME or NME. Of the 4 remaining dogs, one dog (Siberian husky) had a focal lesion in the frontal lobe that showed presence of mass effect, parenchymal contrast enhancement and dural contact. Although abnormalities on CSF-analysis do not exclude neoplastic or vascular disease (REF), this dog had an increased TNCC (35 WBC/mm3) and TP concentration (0.35 g/l) on cisternal CSF analysis. The dog was only 30 months old, and died acutely at home 18 days after diagnosis after initial improvement on immunosuppressive therapy. The second, third and fourth dog (2 cross breeds and an English Springer Spaniel) were 26 – 85 months old at time of diagnosis and had a focal lesion in the piriform lobe (crossbreed) or brainstem (cross breed an English Springer Spaniel). All three dogs had increased TNCC and TP concentrations on cisternal CSF analysis, and all were alive 1095 – 1580 days after diagnosis. All dogs had an acute onset of neurological signs, which might still be compatible with cerebrovascular disease, which might be supported by the long survival without treatment of those dogs. However, in cerebrovascular disease, contrast enhancement should only be visible after 7-10 days in dogs with ischaemic infarcts, and after 6 days to 6 weeks in dogs with haemorrhagic infarcts (Garosi 2012). All dogs with a focal lesion had intracranial imaging within 5 days after onset of neurological signs, and all lesions showed parenchymal contrast enhancement, which was considered less typical for cerebrovascular disease. Neoplastic disease can however not be excluded in those cases, although all 4 dogs were still young at time of diagnosis (2-5y of age) where brain tumors are typically affecting middle-aged to older (over 5 years) dogs and cats, with the majority being greater than 9 years of age (**Dickinson 2014; Snyder and others 2006**).

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

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

Conclusions

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

References

Adamo, P.F., Rylander, H., Adams, W.M. (2007) Ciclosporin use in multi-drug therapy for meningoencephalomyelitis of unknown aetiology in dogs. Journal of Small Animal Practice 48, 486-496.

Alves, L., Gorgas, D., Vandevelde, M., Gandini, G., Henke, D. (2011) Segmental meningomyelitis in 2 cats caused by Toxoplasma gondii. Journal of Veterinary Internal Medicine 25, 148-52.

Barnoon, I., Shamir, M.H., Aroch, I., Bdolah-Abram, T., Srugo, I., Konstantin, L., Chai, O. (2016) Retrospective evaluation of combined mycophenolate mofetil and prednisone treatment for meningoencephalomyelitis of unknown etiology in dogs: 25 cases (2005-2011). Journal of Veterinary Emergency and Critical Care (San Antonio) 26, 116-124.

Beckmann, K., Carrera, I., Steffen, F., Golini, L., Kircher, P.R., Schneider, U., Bley, C.R. (2015) A newly designed radiation therapy protocol in combination with prednisolone as treatment for meningoencephalitis of unknown origin in dogs: a prospective pilot study introducing magnetic resonance spectroscopy as monitor tool. Acta Veterinaria Scandinavica 57, 4-18.

Benjamini, Y., Drai, D., Elmer, G., Kafkafi, N., Golani, I. (2001) Controlling the false discovery rate in behavior genetics research. Behavioural Brain Research 125, 279 – 284.

Bentley, R.T., Burcham, G.N., Heng, H.G., Levine, J.M., Longshore, R., Carrera-Justiz, S., Kopf, K., Miller, M.A. (2014) A comparison of clinical, magnetic resonance imaging an pathological findings in dogs with gliomatosis cerebri, focusing on cases with minimal magnetic resonance imaging changes. Veterinary and Comparative Oncology 19, 1-13.

Cherubini, G.B., Manis, P., Martinez T.A., Lamb, R.L., Capello R. (2005) Utility of magnetic resonance imaging for distinguishing neoplastic from non-neoplastic brain lesions in dogs and cats. Veterinary Radiology and Ultrasound 46, 384-387.

Cherubini, G.B., Platt, S.R., Anderson, T.J., Rusbridge, C., Lorenzo, V., Mantis, P., Capello, R. (2006) Characteristics of magnetic resonance images of granulomatous meningoencephalomyelitis in 11 dogs. Veterinary Record 159, 110-115.

Coates, J.R., Barone, G., Dewey, C.W., Vitale, C.L., Olloway-Azene, N.M., Sessions, J.K., (2007) Procarbazine as adjunctive therapy for treatment of dogs with presumptive antemortem diagnosis of granulomatous meningoencephalomyelitis: 21 cases (1998-2004). Journal of Veterinary Internal Medicine 21, 100-106.

Coates, J.R. & Jefferey, N.D. (2014) Perspectives on meningoencephalomyelitis of unknown origin. Veterinary Clinics of North America Small Animal Practice 44, 1157-1185.

Cooper, J.J., Schatzberg, S.J., Vernau, K.M., Summers, B.A., Porter, B.F., Siso, S., Young, B.D., Levine, J.M. (2014) Necrotising meningoencephalitis in atypical dog breeds: a case series and literature review. Journal of Veterinary Internal Medicine 28, 198-203.

~~Dewey, C.W. (2016). Encephalopathies: disorders of the brian. In *A practical guide to canine and feline neurology, 3rd edition* . Eds C.W. Dewey & R. Da Costa. Blackwell Publishing, Danvers, USA. Pp 141 – 236.~~

Dickinson, P.J. (2014) Advances in diagnostic and treatment modalities for intracranial tumors. Journal of Veterinary Internal Medicine 28, 1165-1185.

Estey, C.M., Scott, S.J., Cerda-Gonzalez, S. (2014) Necrotizing meningoencephalitis in a large mixed-breed dog. Journal of the American Veterinary Medical Association 245, 1274-1278.

Falzone, C., Baroni, M., De Lorenzi, D., Mandara, M.T. (2008) Toxoplasma gondii brain granuloma in a cat: diagnosis using cytology from an intraoperative sample and sequential magnetic resonance imaging. Journal of Small Animal Practice 49, 95-9.

Flegel, T., Boettcher, I.C., Matiasek, K., Oevermann, A., Doherr, M.G., Oechtering, G., Henke, D. (2011) Comparison of oral administration of lomustine and prednisolone or prednisolone alone as treatment for granulomatous meningoencephalomyelitis or necrotizing encephalitis in dogs. Journal of the American Veterinary Medical Association, 238-337-345.

Fliegner, R.A., Holloway, S.A., Slocombe, R.F. (2006) Granulomatous meningoencephalomyelitis with peripheral nervous system involvement in a dog. Australian Veterinary Journal 84, 358-361.

Garosi, L. (2013) Lesion localization and differential diagnosis. In: BSAVA Manual of Canine and Feline Neurology, Fourth edition. Ed Platt SR, Olby NJ. British Small Animal Veterinary Association. Pp25-35.

Garosi, L., Dawson, A., Couturier, J., Matiasek, L., de Stefani, A., Davies, E., Jefferey, N., Smith, P. (2010) Necritzing cerebellitis and cerebellar atrophy caused by Neospora caninum infection: magnetic resonance imaging and clinicopathologic findings in seven dogs. Journal of Veterinary Internal Medicine 24, 571-78.

Garosi, L. (2012). Cerebrovascular accidents. In *Small animal neurological emergenices*. Eds S. Platt & L. Garosi. Manson Publishing, London, UK. Pp 319 – 332.

Granger, N., Smith, P.M., Jeffery, N.D. (2010) Clinical findings and treatment of non-infectious meningoencephalomyelitis in dogs: A systematic review of 457 published cases from 1962 to 2008. The Veterinary Journal 148, 290-97.

Gregory, C.R., Stewart, A., Sturges, B., Demanvelle, T., Cannon, A., Ortega, T., Harb, M., Morris, R.E. (1998) Leflunomide effectively treats naturally occurring immune-mediated and inflammatory diseases of dogs that are unresponsive to conventional therapy. Transplantation Proceedings 30, 4143-4148.

Higginbotham, M.J., Kent, M., Glass, E.N. (2007) Noninfectious inflammatory central nervous system diseases in dogs. Compendium on Continuing Education for the Practising Veterinarian 29, 488-497.

Higgins, R.J., Dickinson, P.J., Kube, S.A., Moore, P.F., Couto, S.S., Vernau, K.M., Sturges B.K., Lecouteur, R.A. (2008) Necrotizing meningoencephalitis in five Chihuahua dogs. Veterinary Pathology 45, 336-346.

Lowrie, M., Smith P.M., Garosi, L. (2013) Meningoencephalitis of unknown origin: investigation of prognostic factors and outcome using a standard treatment protocol. Veterinary Record 172, 527.

Mercier, M. & Barnes Heller, H.L. (2015) Efficacy of glucocorticoid monotherapy for treatment of canine meningoencephalomyelitis of unknown etiology: a prospective study in 16 dogs. Veterinary Medicine and Science 1, 1-7.

Munana, K.R. & Luttgen, P.J., (1998) Prognostic factors for dogs with granulomatous meningoencephalomyelitis: 42 cases (1982-1996). Journal of the American Veterinary Medical Association 12, 1902-1906.

Pakozdy, A., Leschnik, M., Kneissl, S., Gumpenberger, M., Gruber, A., Tichy, A., Thalhammer, J.G. (2009) Improved survival time in dogs with suspected GME treated with ciclosporin. Veterinary Record 164, 89-90.

Park, E.S., Uchida, K., Nakayama, H. (2012) Comprehensive immunhistochemical studies on canine necrotizing meningoencephalitis (NME), necrotizing leucoencephalitis (NLE), and granulomatous meningoencephalomytelisis (GME). Veterinary Pathology 49, 682-692.

Parzefall, B., Driver, C.J., Benigni, L., Davies, E. (2014) Magnetic resonance imaging characteristics in four dogs with central nervous system neosporosis. Veterinary Radiology and Ultrasound 55, 539-46.

Pfohl, J.C. & Dewey, C.W. (2005) Intracranial Toxoplasma gondii granuloma in a cat. Journal of Feline Medicine and Surgery 7, 369-74.

Schatzberg, S.J. (2005) An update on granulomatous meningoencephalitis, necrotizing meningoencephalitis and necrotizing leucoencephalitis. In: Proceedings of the American College of Veterinary Internal Medicine forum 2005, Burnaby, BC, Canada.

Smith, P.M., Stalin, C.E., Shaw, D., Granger, N., Jeffery, N.D. (2009) Comparison of two regimens for the treatment of meningoencephalomyelitis of unknown etiology. Journal of Veterinary Internal Medicine 23, 520-526.

Snyder, J.M., Shofer, F.S., Van Winkle, T.J., Massicotte, C. (2006) Canine intracranial primary neoplasia: 173 cases (186-2003). Journal of Veterinary Internal Medicine 20, 669-675.

Spitzbarth, I., Schenk, H.C., Tipold, A., Beineke, A. (2010) Immunohistochemical characterization of inflammatory and glial responses in a case of necrotizing leucoencephalitis in a French Bulldog. Journal of Comparative Pathology 142, 235-241.

Talarico, L.R. & Schatzberg, S.J. (2010) Idiopathic granulomatous and necrotising inflammatory disorders of the canine central nervous system: a review and future perspectives. Journal of Small Animal Practice 51, 138-149.

Timmann, D., Konar, M., Howard, J., Vandevelde, M. (2007) Necrotising encephalitis in a French Bulldog. Journal of Small Animal Practice 48, 339-342.

Wolff, C.A., Homes, S.P., Young, B.D., Chen, A.V., Kent, M., Platt, S.R., Savage, M.Y., Schatzberg, S.J., Fosgate, G.T., Levine, J.M. (2012) Magnetic resonance imaging for the differentiation of neoplastic, inflammatory, and cerebrovascular brain disease in dogs. Journal of Veterinary Internal Medicine 26, 589-597.

Wong, M.A., Hopkins, A.L., Meeks, J.C., Clarke, J.D. (2010) Evaluation of treatment with a combination of azathioprine and prednisone in dogs with meningoencephalomyelitis of undetermined etiology: 40 cases (2000-2007). Journal of the American Veterinary Medical Association 237, 929-935.

Zarfoss, M., Schatzberg, S., Venator, K., Cutter-Schatzberg, K., Cuddon, P., Pintar, J., Weinkle, T., Scarlett, J., deLahunta, A. (2006) Combined cytosine arabinoside and prednisone therapy for meningoencephalitis of unknown aetiology in 10 dogs. Journal of Small Animal Practice 47, 588-595.

1 **Tables**

2

3 **Table 1**

Variable	**Small/medium breed dogs (n=83)**	**Large breed dogs (n=28)**	**P value/FDR**
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 ($.10^9$/l)	10.6 (3.52 – 32.8)	9.8 (4.66 – 25.1)	0.5888/0.05
Neutrophils ($.10^9$/l)	7.5 (2.4 – 28.3)	7.1 (3.2 – 22.3)	0.4420/0.0429
Lymphocytes ($.10^9$/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^3)	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

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

Table 2

1

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

English Springer Spaniel	**47**	**1**	**yes**	**12**	**0,16**	**Multifocal lesions brainstem**	**72**	**ALIVE**
English Springer Spaniel	**61**	**5**	**no**	**29**	**0,23**	**Multifocal lesions forebrain and brainstem**	**2039**	**ALIVE**
English Springer Spaniel	**39**	**1**	**yes**	**173**	**0,68**	**Focal lesion brainstem**	**1187**	**ALIVE**
English Springer Spaniel	**78**	**2**	**yes**	**NP**	**NP**	**Multifocal lesions forebrain, brainstem and cerebellum**	**700**	**ALIVE**
German Wirehaired Pointer	**10**	**4**	**yes**	**12**	**0,23**	**Multifocal lesions forebrain and brainstem**	**975**	**ALIVE**
Golden Retriever	**75**	**7**	**yes**	**1**	**0,21**	**Multifocal lesions forebrain and brainstem**	**1**	**GME**
Golden Retriever	**60**	**7**	**yes**	**22**	**0,46**	**Multifocal lesions forebrain and brainstem**	**1856**	**ALIVE**
Great Dane	**60**	**2**	**yes**	**40**	**0,1**	**Multifocal lesions forebrain**	**1**	**NP**
Japanese Akita	**20**	**2**	**no**	**51**	**0,41**	**Multifocal lesions forebrain and brainstem**	**1**	**NP**
Labrador	**120**	**13**	**yes**	**8**	**0,1**	**Focal lesion forebrain**	**3**	**NME**
Labrador	**47**	**7**	**yes**	**3**	**0,24**	**Multifocal lesions forebrain and brainstem**	**1**	**NLE**
Labrador	**27**	**7**	**no**	**NP**	**NP**	**Diffuse lesions forebrain**	**184**	**ALIVE**
Labrador	**94**	**3**	**no**	**30**	**0,43**	**Multifocal lesions forebrain and brainstem**	**730**	**ALIVE**
Shar-Pei	**36**	**9**	**yes**	**NP**	**NP**	**Multifocal lesions forebrain**	**2129**	**ALIVE**
Siberian Husky	**30**	**2**	**no**	**68**	**0,35**	**Focal lesion forebrain**	**18**	**NP**
Welsh Springer Spaniel	**89**	**21**	**yes**	**675**	**5,56**	**Multifocal lesions forebrain and brainstem**	**3**	**GME**

1

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

Figure legends

Figure 1

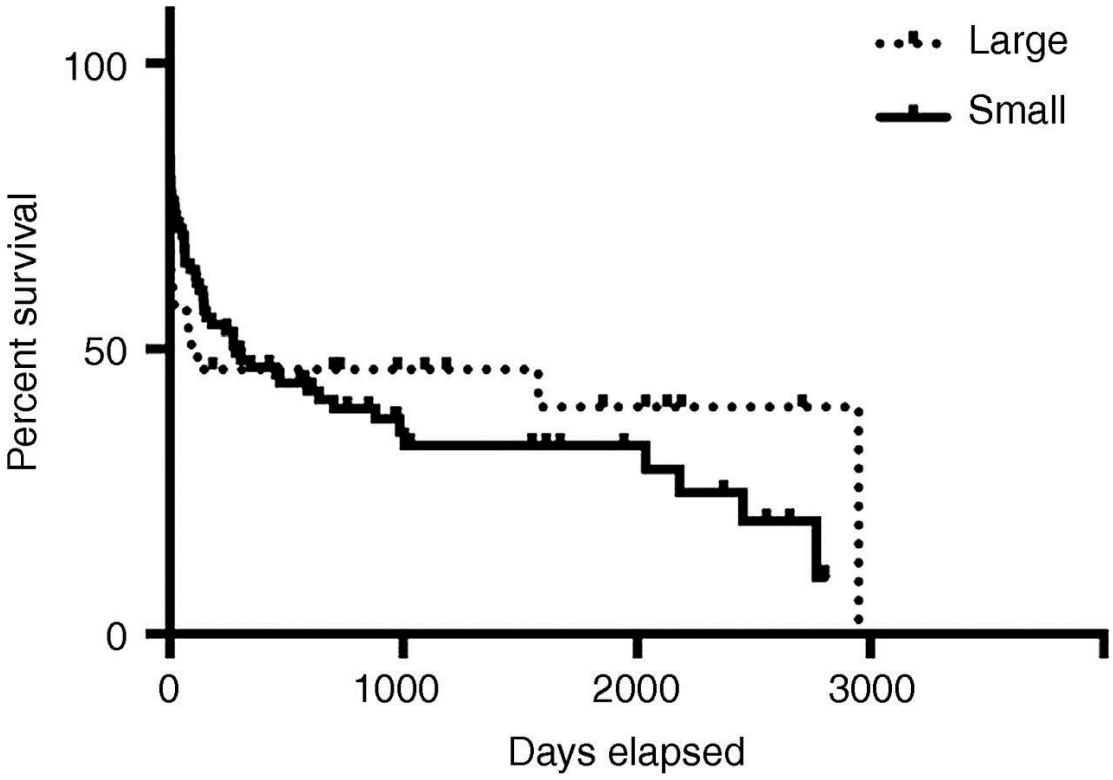

Figure 1: Kaplan-Meier survival curve comparing the percentage of survival in small/medium (full black line) and large (dotted line) breed dogs. Results were censored for dogs that were still alive at time of data capture (single little blocks).