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Prognostic factors for 1-week survival in dogs diagnosed with meningoencephalitis of unknown aetiology

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ABSTRACT

Although long-term outcomes of meningoencephalitis of unknown aetiology (MUA) in dogs have been evaluated, little is known about short-term survival and initial response to therapy. The aim of this study was to evaluate possible prognostic factors for 7-day survival after diagnosis of MUA in dogs. Medical records were reviewed for dogs diagnosed with MUA between 2006 and 2015. Previously described inclusion criteria were used, as well as 7-day survival data for all dogs. A poor outcome was defined as death within 1 week. Of 116 dogs that met inclusion criteria, 30 (26%) died within 7 days of diagnosis. Assessed variables included age, sex, bodyweight, duration of clinical signs and treatment prior to diagnosis, venous blood glucose and lactate levels, white blood cell count on complete blood count, total nucleated cell count/total protein concentration/white blood cell differentiation on cerebrospinal fluid (CSF) analysis, presence of seizures and cluster seizures, mentation at presentation, neuroanatomical localisation, imaging findings and treatment after diagnosis. Multivariate analysis identified three variables significantly associated with poor outcome; decreased mentation at presentation, presence of seizures, and increased percentage of neutrophils on CSF analysis. Despite initiation of appropriate treatment, more than a quarter of dogs died within 1 week of diagnosis of MUA, emphasising the need for evaluation of short-term prognostic factors. Information from this study could aid clinical staff to provide owners of affected dogs with prognostic information.

Introduction

Meningoencephalitis of unknown aetiology (MUA) describes all clinically diagnosed cases of granulomatous meningoencephalitis (GME), necrotising meningoencephalitis (NME) and necrotising leucoencephalitis (NLE) that lack histopathological confirmation (Coates and Jefferey, 2014). A clinical diagnosis can be achieved based on a combination of neurological examination results, magnetic resonance imaging (MRI) findings and cerebrospinal fluid (CSF) abnormalities (Coates and Jefferey, 2014). The exact aetiology and pathophysiology of MUA are currently unknown, but the cornerstone of medical treatment is immunosuppressive therapy. Several treatment protocols using different immunomodulating drugs, resulting in different long-term survival times have been reported (Munana and Luttgen, 1998; Coates et al., 2007; Jung et al., 2007; Granger et al., 2010; Flegel et al., 2011; Beckmann et al., 2015; Barnoon et al., 2016).

Although several studies have focused on long-term survival, little is known about early survival and initial response to therapy of dogs diagnosed with MUA. The primary aim of this study was therefore to evaluate early survival and initial response to immunosuppressive therapy in those dogs. A secondary aim was to investigate possible prognostic factors for 7-day survival after diagnosis of MUA. It was hypothesised that a substantial portion of dogs with MUA would succumb in the first week after diagnosis despite appropriate treatment and monitoring. It was further hypothesised that specific characteristics of the clinical presentation, neurological examination, clinical pathology abnormalities, imaging findings and type of treatment would be associated with 7-day survival in dogs with a presumptive diagnosis of 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 MUA. Dogs were included based on the criteria used by Granger et al. (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) if 7-day follow-up information was available. Dogs with histopathological confirmation of MUA only needed to fulfill inclusion criteria (1) and (5). In this study, the term MUA was used for all dogs included in the study, including those with histopathological confirmation of GME, NME or NLE.

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Dogs were excluded if: (1) 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 (4) if positive test results were found on serology or PCR examination for canine distemper virus (CDV), *Toxoplasma gondii* or *Neospora caninum*.

Information retrieved from the medical records included breed, gender, age at diagnosis, sex, bodyweight, neurological examination results and neuroanatomical localisation, duration of clinical signs and treatment prior to diagnosis, presence of concurrent disease, results of complete blood count (CBC) and biochemistry profile, results of CSF analysis including total nucleated cell count (TNCC), white blood cell differentiation and total protein (TP) concentration, lactate and glucose concentration on venous blood gas analysis, treatment received and 7-day survival time.

Dogs were considered small or medium breed if bodyweight was <15 kg, and large breed if bodyweight was ≥15 kg. Mentation was classified as bright alert responsive (BAR), quiet alert responsive (QAR), obtundation, stupor or coma, representing decreasing mental status. Possible neuroanatomical localisations included forebrain, brainstem or cerebellum. Dogs with vestibular signs attributable to a brainstem-associated lesion were diagnosed with central vestibular signs. If two or more CNS regions appeared to be affected on neurological examination, a multifocal neuroanatomical localisation was made, whereas in dogs with only one region affected, a focal neuroanatomical localisation was made. MRI was performed under general anaesthesia with a 1.5 T magnet (Intera, Philips Medical Systems). All images were reviewed by a board certified neurologist (SDD) using Osirix Dicom viewer (Osirix Foundation, V.5.5.2). The reviewer was blinded to results of the neurological examination, outcome after 7 days and histopathological findings. 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). 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). For CSF analysis, site of collection (cisternal or lumbar), TNCC, TP and cytological differentiation were recorded. A TNCC < 5 cells/mm^3 was considered normal. Protein concentration was considered normal for a cisternal collection if <0.25 g/L and for a lumbar collection if <0.4 g/L (Dewey et al., 2016).

Treatment and follow-up

For all dogs, the specific treatment protocol was recorded (corticosteroids with or without cytosine arabinoside). During hospitalisation, all dogs underwent at least one daily general physical examination and a complete neurological examination by a board-certified neurologist or a neurology resident. Neurological examination results and response to treatment (improvement, deterioration, or static) were systematically recorded on the kennel sheets. Follow-up information for the first 7 days after diagnosis was collected from medical records. If dogs were discharged within the first 7 days, medical records were searched for the presence of a re-examination or owner communication to confirm the dog was alive. Dogs were excluded from the study if this information was not available. A successful outcome was defined as survival for at least 7 days after diagnosis of MUA, while an unsuccessful outcome was defined as death in the first 7 days after diagnosis. For dogs that died in the first week after diagnosis, information on whether dogs were euthanased at the owner's request after diagnosis without treatment, they failed to recover from general anesthesia after MRI, or they died or were euthanased due to progression of disease after recovery from general anesthesia was recorded. Dogs that did not survive general anaesthesia or were euthanased at the owner's request after diagnosis without treatment were not included for further analysis.

Statistical analysis

Outcome was defined as dead or alive 7 days after diagnosis. Data analysis was performed using a statistical software package (Prism, GraphPad Software). A Mann–Whitney *U* test was used to compare age, weight, duration of clinical signs prior to diagnosis, venous blood glucose and lactate levels, white blood cell (total, neutrophil and lymphocyte) count on CBC, TNCC/TP/neutrophil percentage in CSF, between dogs that were dead or alive 1 week after diagnosis. A Fisher's exact test was used to compare differences in sex, treatment prior to diagnosis, presence of seizures and cluster seizures, mentation (BAR, QAR, obtundation, stupor, coma), neuroanatomical localisation (multifocal, forebrain, brainstem, central vestibular), treatment after diagnosis (steroids, cytosine arabinoside, mannitol) and imaging findings (lesion localisation, meningeal or parenchymal contrast enhancement, mass effect, brain herniation, flattening gyri/sulci, rostral or caudal transtentorial herniation, foramen magnum herniation) between dogs that were dead or alive 1 week after diagnosis.

A binary response mixed model was carried out using SPSS (Statistical Package for the Social Sciences v. 21.0.1, SPSS). The binary response variable was whether the dog was dead or alive 7 days after diagnosis. Factors found to be significant at the univariate level were taken forward for multivariate analysis. Bodyweight, duration of clinical signs, lactate concentration on venous blood gas analysis, TNCC on CSF analysis and percentage of neutrophils in CSF were modeled as continuous fixed effects. Mentation was modeled as a categorical fixed effect, and the presence of seizures, cluster seizures and cytosine arabinoside administration were modeled as binomial fixed effects. Breed was included as a random effect, with cross breeds coded plainly as 'cross breed' due to unknown parentage. This random effect took into account the genetic non-independence of multiple members of the same breed in the study population, and possible demographic and environmental factors. All models were checked for multicollinearity, identified from inflated standard errors in the models, and thus avoided. Model fit was assessed using the deviance and Akaike's information criterion. Numeric variables were expressed as median and interquartile range. Values of $P < 0.05$ were considered significant. Receiver operating characteristic (ROC) analysis was performed to examine the performance of the significant continuous variables on multivariate analysis as an indicator of prognosis, by determining the power of the test by measuring the area under the curve (AUC). A perfect test has an AUC value of 1.0; an AUC of 0.5 means the test performs no better than chance.

Results

Signalment

One hundred and sixteen dogs met the inclusion criteria and were included in the study. Eighty-seven dogs (75%) were small or medium breed and 29 dogs (25%) were large breed. Median age at presentation was 52.5 months (4–146 months) and median bodyweight was 9.2 kg (1.65–94 kg). Fifty dogs (43%) were female, of which 30 were neutered, compared to 66 males (57%), of which 40 were neutered. Median duration of clinical signs before diagnosis was 7 days (range 1–180 days). Twenty dogs (17%) were treated with anti-inflammatory doses of glucocorticoids (doses ranging from 0.5 to 1 mg/kg administered every 12–24 h) prior to diagnosis, with a median duration of 3.5 days (range 1–90 days).

Neurological examination

Mentation was classified as BAR in 30 dogs (26%), QAR in 21 dogs (18%), obtundation in 59 dogs (51%) and stupor in six dogs (5%). No dogs presented comatose. Twenty-nine dogs (25%) presented with seizures, of which 20 dogs (69%) presented with cluster seizures and two dogs (31%) with status epilepticus. Sixty-six dogs (57%) presented with multifocal neurological signs, 50 dogs (43%) with focal neurological signs. Of the latter, 39 dogs (78%) presented with focal forebrain signs, eight dogs (16%) with focal brainstem signs, two dogs (4%) with focal cerebellar signs, and one dog (2%) with central vestibular signs.

Diagnostic findings

Results of CBC and biochemistry profile were available in 97 dogs (84%). Leucocytosis was present in 13 dogs (13%) and lymphopenia in 32 dogs (33%). Serology and/or PCR analysis for *Toxoplasma gondii*, *Neospora caninum* and canine distemper virus were available and negative in 82 dogs (71%). Lactate and glucose concentrations on venous blood gas analysis were available in 49 dogs (42%), revealing an increased lactate and/or glucose concentration in nine (18%) and 12 (24%) dogs, respectively. CSF analysis was not performed in 20 dogs (17%); it revealed no abnormalities in three dogs (3%); and a pleocytosis in the remaining 93 dogs (80%). In the three dogs with normal TNCCs, complete necropsy revealed GME ($n = 1$), NME ($n = 1$) or NLE ($n = 1$). For the dogs with a pleocytosis ($n = 93$), median TNCC was 80 WBC/mm^3 (6–2560 WBC/mm^3). For the dogs that died in the first week after diagnosis, median percentages of lymphocytes, neutrophils and monocytes/macrophages were 54%, 5% and 24%, respectively, compared to dogs that survived the first week after diagnosis, where percentages were 66%, 1% and 23%, respectively. Pretreatment with glucocorticoids did not significantly influence the TNCC on CSF analysis ($P = 0.9116$).