MAGNETIC RESONANCE IMAGING AND PATHOLOGIC FINDINGS ASSOCIATED WITH NECROTIZING ENCEPHALITIS IN TWO YORKSHIRE TERRIERS

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Two young adult Yorkshire terriers had neurologic signs consistent with forebrain and brainstem involvement or forebrain involvement alone. On magnetic resonance imaging studies there were asymmetric bilateral lesions mainly in the cerebral cortex, and in the diencephalon. These areas were hyperintense on T2-weighted and FLAIR images, but hypointense or isointense on T1-weighted images. Lesions had a varying degree of contrast enhancement. Areas which were isointense on T1-weighted images had no contrast enhancement or only foci of contrast enhancement. Lesions with hypointensity in T1-weighted images had no enhancement or more frequently ring-like enhancement around the lesion. Necrotizing encephalitis was confirmed pathohistologically in both dogs. The degree of contrast enhancement appeared to be related to the degree of lymphohistiocytic inflammation on histologic examination. Veterinary Radiology & Ultrasound, Vol. 47, No. 3, 2006, pp 260–264.

Key words: contrast enhancement, magnetic resonance imaging, necrotizing encephalitis, Yorkshire terrier.

Introduction

Necrotizing encephalitis of Yorkshire terriers was first described in 1993. Since then several case reports have been published. Necrotizing encephalitis is a sporadic nonsuppurative encephalitis affecting mostly young adults. Both sexes seem to be equally affected. Clinical signs depend on the lesion localization, but central vestibular signs in combination with diffuse forebrain signs such as reduced mentation, visual deficits as well as seizures predominate. This disease has a fatal outcome in most reports. Survival after established diagnosis varies between 3 and 18 months.

Clinical signs are consistent with multifocal intracranial disease, which is not specific for necrotizing encephalitis. Further diagnostics such as cerebrospinal fluid (CSF) analysis and brain imaging have been used to establish a final diagnosis. CSF findings may include mononuclear pleocytosis and protein elevation. Computed tomographic imaging characteristics of necrotizing encephalitis have been described, but to our knowledge there are only reports of magnetic resonance imaging (MRI) changes in histologically confirmed necrotizing encephalitis in four Yorkshire terriers. We describe the clinical course, CSF changes, and MR findings in two dogs with histologically confirmed necrotizing encephalitis being referred to the Department of Small Animal Medicine of the University of Leipzig.

Case History Reports

Dog 1 was a 3-year-old intact male Biewer Yorkshire terrier with a history of vision loss and walking into objects for 2 weeks. The owner consulted the emergency service because of an acute gasping for breath, shaking, salivation, and involuntarily loss of feces and urine consistent with a generalized clonic seizure for the past 2 h.

On the following day T1 and T2 weighted as well as T2/fluid attenuated inversion recovery (FLAIR) and contrast-enhanced T1-weighted 3-mm thick images of the brain with an 0.3-mm interslice gap were obtained in transverse, sagittal, and dorsal planes using a 0.5-T superconducting magnet. Contrast-enhanced T1-weighted images were obtained immediately after an intravenous bolus of gadopentetate dimeglumine of 0.1 mmol/kg. The T1-weighted scan sequences used a repetition time (TR) of 550 ms and an echo time (TE) of 10 ms, the FLAIR scans a TR and TE of 5000 and 100 ms and the T2-weighted scans a TR and a TE of 2250 and 100 ms, respectively. In both the T2-weighted sequences and the FLAIR sequences an irregular hyperintensity of the entire left cortical gray matter and subcortical white matter was present (Fig. 1A and B). Another area of hyperintensity was seen within the left
thalamus at the level of the pretectal nuclei which was more obvious on FLAIR images. Additionally, on the FLAIR images the right cingulate gyrus had a hyperintense signal (Fig. 1B). All these lesions appeared hypointense to surrounding brain on the T1-weighted images (Fig. 1C). Slight peripheral enhancement after contrast medium administration could be seen, which was most obvious in the left occipital lobe (Fig. 1D).

CSF was obtained via atlanto-occipital puncture. On CSF analysis a mononuclear pleocytosis of 31 nucleated cells per microliter (reference range ≤ 5/μl) was found. The protein content was 0.55 g/l (reference range ≤ 0.25 g/l).

The dog did not improve with treatment and was euthanized 2 days after presentation on the owner’s request. A pathologic examination of the brain was performed.

Grossly there were bilaterally large areas of subcortical liquefaction within the parietotemporal lobes. Malacic foci were most prominent in corona radiata and centrum semiovale and consisted of ongoing degeneration with vascular prominence, marked lymphohistiocytic infiltrations, glial activation, multiple gitter cells and gemistocytes, and quiescent burnt-out lesions characterized by cavitation, less prominent vasculature, advanced gliosis, and absence of inflammatory and gitter cells. Lesions with pronounced chronicity were surrounded by a sclerotic neuropil. Histologically, the pedunculi of the cerebellum had diffuse hypercellularity and multifocal microvascular bleeding extending into dorsal aspects of the brain stem. Pyramidal cell layers of both hippocampi revealed abundant eosinophilic nerve cell necroses. Hippocampal lesions were consistent with the seizure activity. Histologic features were typical for necrotizing encephalitis and not for an infectious disease. However, an immunohistochemical screening for canine distemper virus, *Toxoplasma gondii* and *Neospora caninum* was performed routinely. Thus, infection by these three common agents could be ruled out.
Dog 2 was a 5-year-old intact female Yorkshire terrier referred for a head turn and circling to the left with an acute onset 1 week before presentation. There was a reduced mental status and a lateroflexion of the neck to the left together with constant circling to the left. Conscious proprioception was absent in the right forelimb. The menace response was absent in the right eye. The dog did not have any vision on this side, as evaluated by a cotton ball test. The pupillary light reflexes were normal on both sides. These signs were consistent with a left-sided forebrain lesion.

An MR study was performed using the same sequences as in the preceding dog. In addition, a turbo inversion recovery (TIR) sequence was obtained with a TR of 3000 ms and a TE of 20 ms. Three localizations with altered signal intensities could be visualized. At the level of the left thalamus lesions could be seen in the caudate nucleus, the lateral geniculate body, and the thalamocortical projection fibers. The ipsilateral internal capsule was partially affected as well. The left corona radiata had altered signal intensity which extended within the subcortical white matter up to the frontal lobe. In addition, the subcortical white matter of the left frontal lobe was affected. All lesions described above were hyperintense on T2-weighted and FLAIR images and had reduced signal intensity on T1-weighted images. In the TIR-sequences the lesions within the thalamus appeared as distinct hypointense areas. The frontal lesion appeared as a hypointense area on the TIR sequence involving only the subcortical white matter (Fig. 2A). The contrast studies revealed a ring enhancement around the lesions within the frontal lobe and caudate nucleus, whereas the other lesions did not have any accumulation of contrast medium (Fig. 2B and C).

The CSF obtained by atlanto-occipital puncture was characterized by a very mild monocytic pleocytosis of six nucleated cells per microliter (reference range ≤5/μl) with

![Fig. 2. Magnetic resonance images of the brain and a corresponding picture of the brain of a Yorkshire terrier with necrotizing encephalitis (dog 2). Images A and B have the same frontal brain area on a transverse turbo inversion recovery sequence (A) and contrast enhanced T1-weighted (B) image with strong enhancement around the right frontal lesion and no enhancement around the lesion on the opposite side. The brain (D) has multifocal cystic cavitations confined to the subcortical white matter. On a transverse T1-weighted image of the brain at the level of caudate nucleus, a mild ring enhancement around the hypointense core can be seen (C).](image-url)
a protein concentration of 0.32 g/l (reference range ≤ 25 g/l).

The patient was euthanized the next day on the owner’s request, because of suspected necrotizing encephalitis, which usually carries a poor long-term prognosis.

The brain had multifocal cystic cavitations confined to the subcortical white matter (Fig. 2D). Moreover, soft discolored foci were observed in the left frontal corona radiata and left telodiencephalic region. The latter mainly involved the internal capsule and extended from caudate nucleus to thalamus and lateral geniculate body in an oblique direction. Cavitary lesions contained gliovascular trabecules only, while lesions that exhibited a ring enhancement were dominated by a marked lymphohistiocytic inflammation with tissue necrosis, activated gitter cells and gemistocytes, moderate gliosis, and a marked vascular prominence. Histologic features were typical for necrotizing encephalitis and not of an infectious disease. However, an immunohistochemical screening for canine distemper virus, T. gondii and N. caninum was performed routinely. Thus, infection by these three common agents could be ruled out.

Discussion

To our knowledge, there are only four single reports describing MRI characteristics of necrotizing encephalitis in Yorkshire terriers. The diagnostic work up in these four dogs did not include CSF analysis, which seems to be mandatory in inflammatory CNS disease. We are describing two additional patients. Both patients had clinical, cerebrospinal fluid, and MRI findings as described in Yorkshire terriers with necrotizing encephalitis. The pathohistologic findings confirmed the presumptive diagnosis. The clinical signs at presentation such as decreased mentation, head pressing, and central blindness were consistent with a forebrain lesion. These neurologic deficits appeared in combination with brainstem signs such as ataxia, nystagmus, and circling in one dog, whereas the head turn and circling to the left in other dog could be related to the forebrain lesion alone. This lesion localization seems to be in slight contrast to the first description of six Yorkshire terriers with necrotizing encephalitis, where brainstem involvement was more consistent.1

CSF analysis was limited in one dog because of the small amount of fluid obtained. Nevertheless, total protein was slightly elevated in both dogs. The cell count was only marginally elevated in one dog and slightly elevated in the other. The cell differentiation was characterized by lymphocytes between 5% and 28% and monocytes between 69% and 95%. These findings are comparable with results found in a series of three Yorkshire terriers with necrotizing encephalitis. Those patients had between 3 and 107 nucleated cells per microliter and protein concentrations between 0.30 and 0.42 g/l. Nucleated cell differentiation was between 95% and 100% mononuclear cells on CSF analysis. Nucleated cell counts between 12 and 76/μl were found in the CSF in another series of six Yorkshire terriers. These pleocytoses consisted of monocytic and lymphocytic cells.

On MR images we found lesions that allow diagnosing necrotizing encephalitis with a high degree of suspicion because of lesion localization, lesion appearance in different sequences, and contrast enhancement. Both dogs had multiple asymmetric bilateral forebrain lesions. The thalamus was affected in both dogs, whereas the cerebrum was affected to varying degree from only mildly affected tissue to lesions involving an entire cerebral hemisphere. The cerebral lesions mainly affected the subcortical white matter, but involved the cortex in some locations as well. On T2 weighted and FLAIR sequences the lesions were hyperintense, whereas they appeared iso- to hypointense on T1-weighted images. Imaging characteristics of T2 hyperintensity and T1 hypointensity usually indicate a cystic lesion. Using FLAIR sequences the true extent of the cystic lesion and the associated edema can be separated from CSF in the ventricular system. A TIR sequence was used in one dog to allow better differentiation between subcortical white matter and cortical gray matter involvement.

The lesions had a varying degree of contrast enhancement. Areas which were isointense on T1-weighted images had no contrast enhancement or only focal regions of contrast enhancement. Lesions with T1 hypointensity had no enhancement or more frequently ring-like enhancement. The degree of contrast enhancement correlated with the degree of lymphohistiocytic inflammation on histologic examination. Areas of contrast enhancement with marked inflammation could indicate more active lesions, whereas cavitary lesions without contrast enhancement or ring-like enhancement only could correspond with a more chronic stage of the same disease. The brain of one patient may exhibit different degrees of contrast enhancement around lesions that look similar on T1-weighted and T2-weighted images.

Even though the MR images revealed multifocal lesions in both dogs, not all lesions that were evident on gradient echo sequences, which are the most sensitive for detecting brain hemorrhage in dogs.9

In one of four previously described Yorkshire terriers with necrotizing encephalitis, where MRI characteristics
have been described, unilateral dilatation of a lateral ventricle was the only obvious pathologic change.\(^6\) In the second dog, bilateral asymmetric hydrocephalus was seen together with a midline shift because of assumed unilateral brain atrophy.\(^3\) In addition, there was a hyperintense signal in the corona radiata and internal capsule on the side of the dilated lateral ventricle. Pathologic contrast enhancement was not seen. In the third dog, there were similar MRI characteristics as in our dogs with regard to signal intensity on T1- and T2-weighted images, whereas contrast enhancement was seen only slightly and inconsistently.\(^5\) A correlation between contrast enhancement pattern and prognosis in dogs with different types of steroid responsive meningoencephalitis has been found with ring enhancement around a hypointense core being associated with poor prognosis.\(^10\) Taking all confirmed examples of necrotizing encephalitis in Yorkshire terriers into consideration, contrast enhancement does not seem to be an indicator for prognostic outcome, since the contrast enhancement in all euthanized dogs varied from no enhancement to strong ring-like enhancement.

The major differential diagnoses for necrotizing encephalitis in Yorkshire terriers, in addition to infectious causes, are subacute necrotizing encephalomyelopathy, granulomatous meningoencephalitis as well as a vascular lesion.\(^11,12\) Infectious encephalitis as well as granulomatous meningoencephalitis may have similar MRI characteristics with multifocal inflammatory lesions as seen in necrotizing encephalitis.\(^5\) Nevertheless, well-circumscribed lesions corresponding to necrotic brain areas being clearly hypointense on T1-weighted images and hyperintense on T2-weighted images may not be obvious. Contrast enhancement may vary from uniform to heterogeneous or ring like.\(^9\) In addition, dogs with granulomatous meningoencephalitis may have a midline shift due to a focal mass effect, which has not been seen in any of the dogs with confirmed necrotizing encephalitis.\(^12\) The other major differential diagnosis, subacute necrotizing encephalomyelopathy, is a neurodegenerative disorder resembling human Leigh syndrome. Lesions are restricted to the CNS. The most consistent findings are grossly visible bilateral and symmetrical cavitated foci in the basal nuclei, midbrain, pons, and medulla.\(^13\) It has been proposed that Leigh syndrome represents the response of the developing CNS to energy deprivation.\(^14\) MRI changes in subacute necrotizing encephalomyelopathy are described for the Alaskan Husky. T2-weighted images are characterized by bilateral hyperintensity in the brainstem, extending from the thalamus to the medulla. These lesions appear hypointense without contrast enhancement on T1-weighted images.\(^15\)

MRI is a valuable tool for diagnosing necrotizing encephalitis. Taking neurolocalization and MR imaging characteristics, including existence of cavitary lesions and contrast enhancement pattern, into consideration, a strong presumptive clinical diagnosis of necrotizing encephalitis should be possible in Yorkshire terriers with typical clinical signs.

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