Clinical presentation and magnetic resonance imaging findings in a juvenile dog with unilateral hydrocephalus and presumed periventricular encephalitis

Klinische presentatie en diagnose met behulp van MRI van unilaterale hydrocefalus en een vermoeden van periventriculaire encefalitis bij een jonge hond

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ABSTRACT

A four-month-old English bulldog presented with an acute onset of facial twitching, head tilt and abnormal mentation. Neurological examination was consistent with a multifocal brain lesion. Hematology and biochemistry were unremarkable and MR imaging of the brain revealed marked enlargement of the left lateral ventricle with associated calvarial enlargement and periventricular T2W and fluid-attenuated inversion recovery (FLAIR) lesions with moderate contrast enhancement. Cerebrospinal fluid (CSF) analysis revealed a moderate mixed mononuclear pleocytosis and infectious disease testing returned negative. The diagnosis of left unilateral internal hydrocephalus and presumed periventricular encephalitis was made. The patient was treated with prednisolone and phenobarbitone with successful outcome despite the poor prognosis. This is the first report of unilateral hydrocephalus and periventricular encephalitis with MR imaging in a dog.

SAMENVATTING

Een vier maanden oude Engelse buldog werd aangeboden met klachten van acute faciale spiertrekkingen, scheve kopstand en een abnormaal bewustzijn. Het neurologisch onderzoek was indicatief voor een multifocale hersenaandoening. Het hematologisch en biochemisch onderzoek was normaal. Magnetische resonantie van de hersenen onthulde een uitgesproken vergroting van de linker laterale ventrikel, met bijkomend een vergroting van het calvarium op dit niveau. Er waren ook periventriculaire letsels op T2W- en FLAIR-beelden zichtbaar met een matige contrastopname. Analyse van het cerebrospinale vocht toonde matig gemengde, mononucleaire pleiocytose en het testen op infectieziekten kwam negatief terug. De meest waarschijnlijke diagnose was unilaterale interne hydrocefalus veroorzaakt door periventriculaire encefalitis. Ondanks de slechte prognose werd de patiënt succesvol behandeld met prednisolone en fenobarbital. Dit is de eerste beschrijving van unilaterale hydrocefalus met vermoedelijke periventriculaire encefalitis bij een hond gediagnosticeerd met behulp van MRI.

INTRODUCTION

Hydrocephalus is defined as an active dilation of the ventricular system in the brain due to insufficient movement of cerebrospinal fluid (CSF) from the ventricles to its sites of absorption (Rekate et al., 2009). Hydrocephalus usually develops due to an interruption of CSF flow or reduced absorption, and rarely, due to excessive production. It can be classified as congenital or acquired, obstructive and non-obstructive, but also as internal, when there is ventricular dilation with CSF accumulation, and external, when there is dilation of the subarachnoid space with CSF accumulation. The term compensatory hydrocephalus

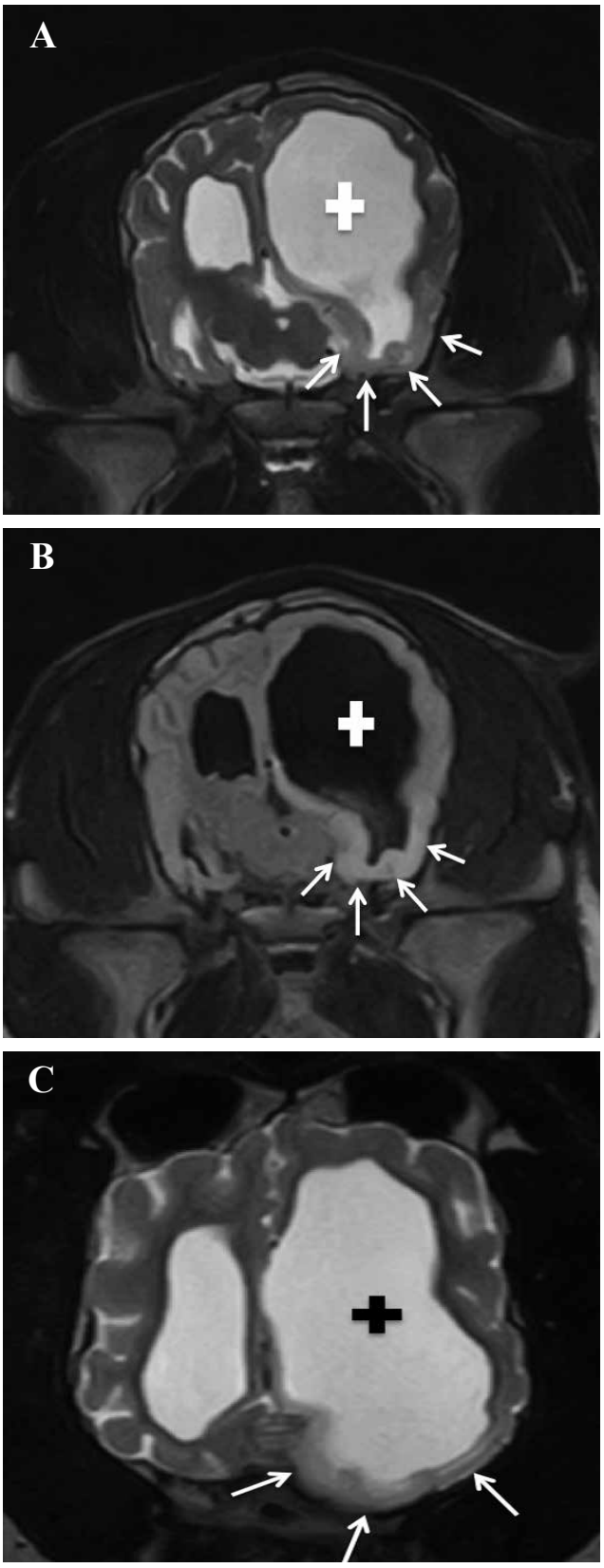

Figure 1. MRI images of the brain: T2W SE and FLAIR transverse sequences the level of the geniculate nuclei (a, b) and T2W SE dorsal image (c). All show the marked ventricular asymmetry with a dilated left lateral ventricle (+). T2W SE and FLAIR periventricular hyperintensities on the left ventricle (white arrows). Black arrows show compression of the brainstem due to the dilated lateral ventricle. Left is on the right of the image.

is also used to describe loss of brain parenchyma being replaced by CSF (De Lahunta and Glass, 2009, Przyborowska et al., 2013, Estey and et al., 2016). Very small (toy) and brachycephalic breeds are overrepresented with this condition, which is usually congenital and affects the ventricles bilaterally (Ryan et al., 2014). An association between hydrocephalus and periventricular encephalitis has been previously reported in juvenile dogs and in a fox (Higgins et al., 1977; Cantile et al., 1997; Mandara et al. 2007). It carries a guarded to poor prognosis, and although an infectious cause has been suspected, the underlying cause remains unknown. The majority of the reported cases were diagnosed on gross and histopathologic examination of the brain at necropsy, and there is only one report of diagnostic imaging of this disease, which was treated successfully with a combination of medical and surgical management (Dewey, 2002). To the authors' knowledge there are no other reports of successful treatment of this disease and there are no reported magnetic resonance imaging (MRI) findings. In this article, a juvenile English bulldog with unilateral hydrocephalus and presumed periventricular encephalitis is described.

CASE DESCRIPTION

A four-month-old, male, entire English bulldog was presented to the Neurology Service of a referral hospital with a two-day history of obtundation, facial twitching and hypersalivation. The dog had no history of exposure to toxins and the only treatment he had received was diazepam intravenously for the management of focal seizures at the referring veterinarian. The patient was fully vaccinated and was up to date with anti-parasitic preventative treatment.

Blood work performed prior to referral revealed changes consistent with young age [ALP 123 mmol/L (reference range, 12-83mmol/L), phosphate 2.88 mmol/L (reference range, 0.60-1.80 mmol/L)]. The remainder of the biochemistry and hematology were within the reference range.

On presentation, the puppy was lethargic. Rectal temperature was increased (40.6 °C). Pulmonary and cardiac auscultations, as well as abdominal palpation, were normal. Body weight was 17.5 kg. Neurological examination performed by a board certified neurologist revealed mild obtundation and compulsive walking with mild proprioceptive ataxia in all limbs. The patient had a mild head tilt to the right. Cranial nerve examination revealed bilateral facial twitching, absent menace response on the right side with normal palpebral and pupillary light reflexes bilaterally. No other cranial abnormalities were observed. Postural reactions were delayed on the right side. Segmental spinal reflexes were intact and spinal palpation was unremarkable. Based on the above findings, a multifocal brain lesion (involving the left forebrain and central vestibular system on the right side) was suspected.

Blood work, including biochemistry, complete blood cell count and fasting ammonia was repeated and all parameters were within normal limits.

An MRI scan of the brain was performed under general anesthesia (0.4T Aperto MRI, Hitachi, Tokyo, Japan). The following sequences and parameters were performed in 3mm slices: T2-weighted spin-echo (T2W SE) transverse (TR 2505, RE 112), T2W spin-echo sagittal (TR 3690, TE 120), T2W spin-echo dorsal (TR 4182, TE 120), FLAIR transverse (TR 8359, TE 87), T2* transverse (TR 656, TE 50), T1W spin-echo transverse pre- and post-Gadolinium (Multihance, Gadobenate dimeglubine 0.1ml/kg) (TR 640, TE 14).

The MR images were reviewed by a board certified radiologist and revealed an asymmetric appearance of the calvarium, probably secondary to a markedly enlarged left lateral ventricle (LV) (Figure 1). The ventricle/brain index on that side was 0.72. The left lateral ventricle occupied approximately 85% of the left side of the brain parenchyma (LV height 48mm, height skull 56mm), produced moderate to marked mass effect with deviation of the midline to the right and secondary atrophy of the cerebral cortex and white matter involving the parietal, temporal and occipital lobes on the left side. There was also moderate compression of the fourth ventricle, the ipsilateral lateral and medial geniculate nuclei, and the rostral colliculi. There were diffuse periventricular T2W and FLAIR hyperintensities around the abnormal left ventricle, as well as in the ipsilateral piriform lobe (Figures 1 and 2). There were no signs of caudal cerebellar or transtentorial herniation. T1W images after contrast administration revealed moderate peri-

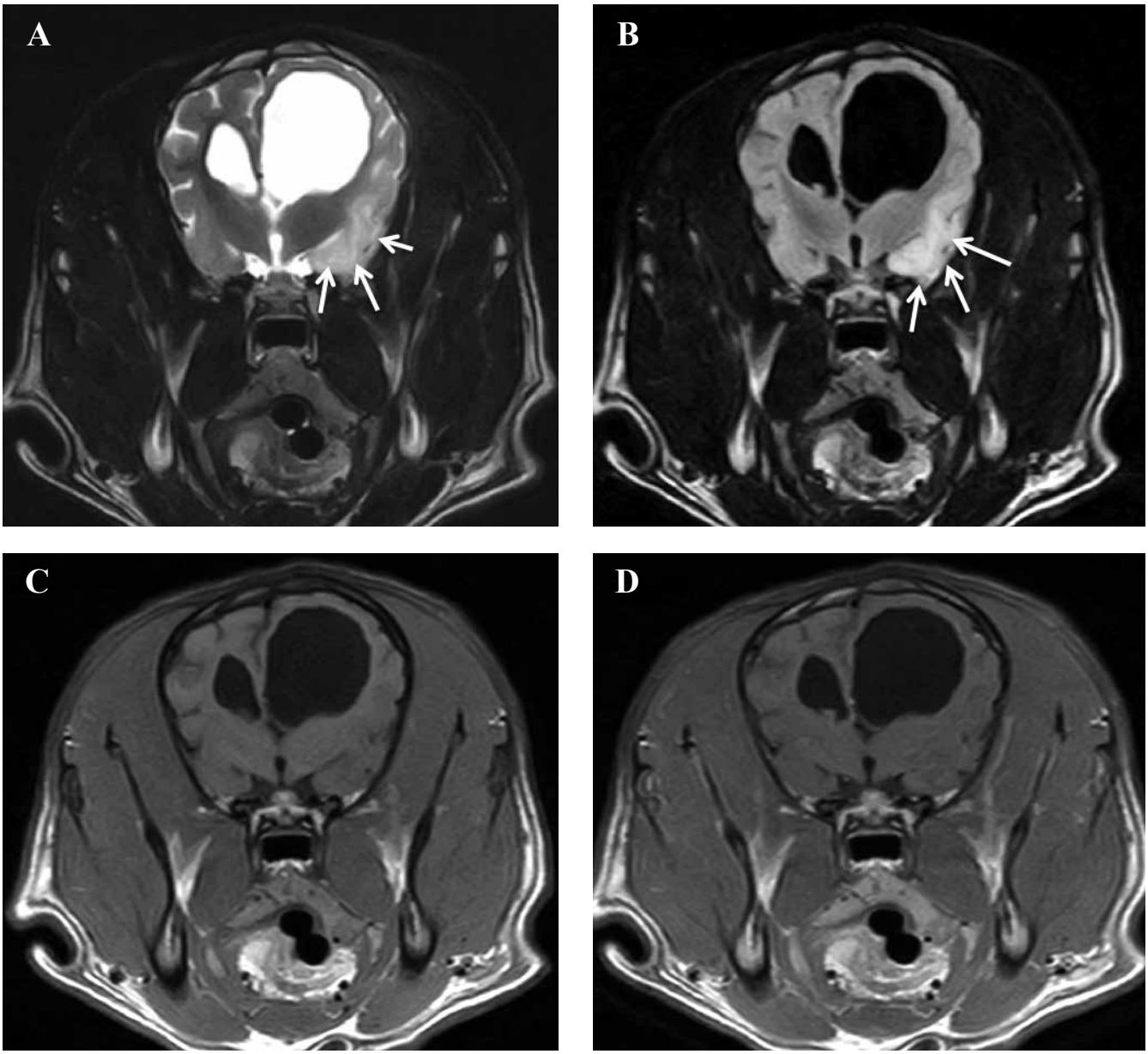

Figure 2. MRI mages on transverse plane at the level of the interthalamic adhesion [T2W SE (a), FLAIR (b), T1W SE (c), T1W SE+ Gadolinium]. They show the unilateral left sided hydrocephalus and T2W left piriform lobe hyperintensities with no contrast enhancement (white arrows). Left is on the right of the image.

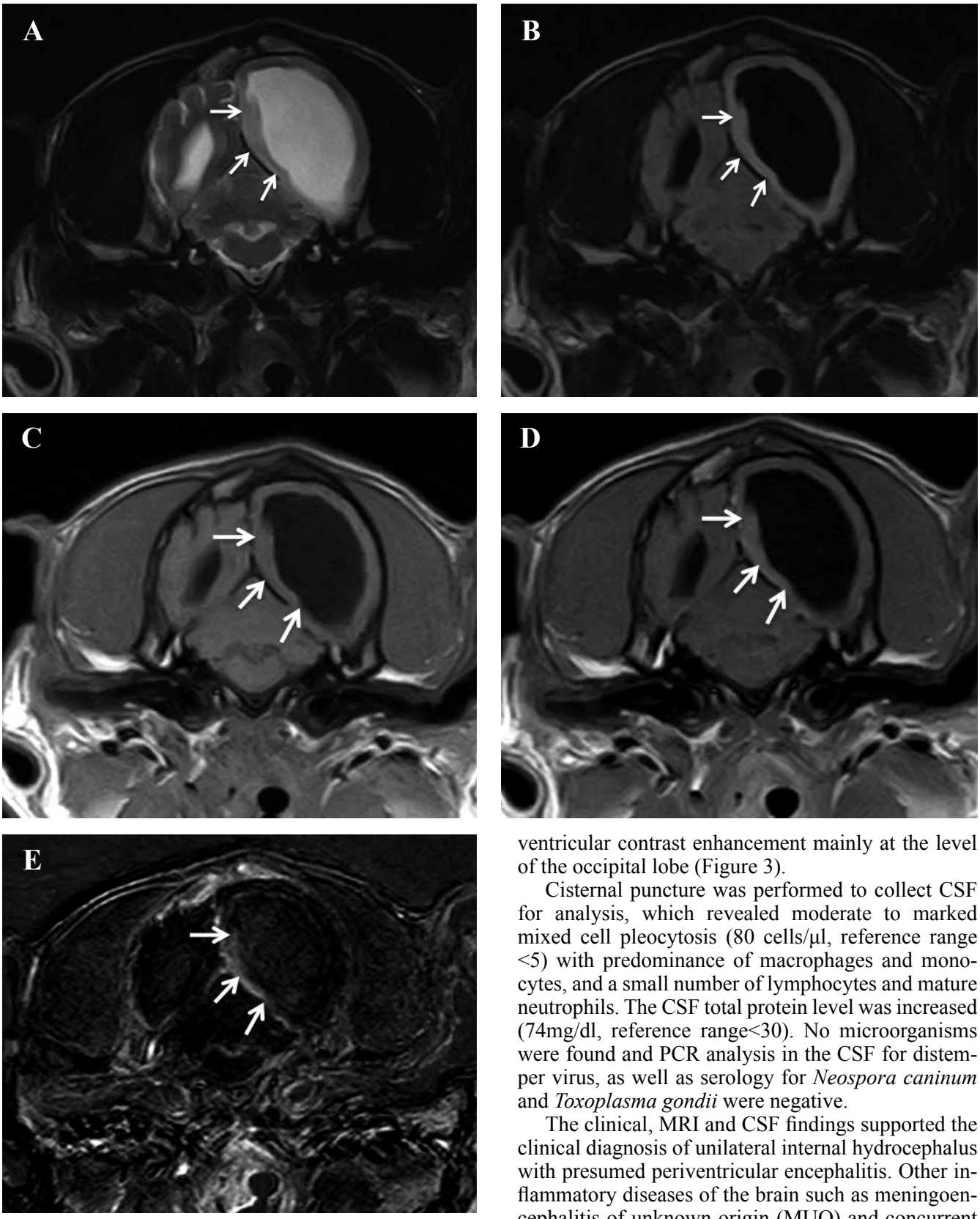

Figure 3. MRI images on transverse plane, including T2W SE (a), FLAIR (b), T1W SE(c), T1W SE+ Gadolinum (d) and substraction (e) sequences of the head at the level of the occipital lobe, revealing periventricular T2W and FLAIR hyperintensities (white arrows), which were isointense on T1W image and enhanced after contrast administration (white arrows). Left is on the right of the image.

ventricular contrast enhancement mainly at the level of the occipital lobe (Figure 3).

Cisternal puncture was performed to collect CSF for analysis, which revealed moderate to marked mixed cell pleocytosis (80 cells/µl, reference range <5) with predominance of macrophages and monocytes, and a small number of lymphocytes and mature neutrophils. The CSF total protein level was increased (74mg/dl, reference range<30). No microorganisms were found and PCR analysis in the CSF for distemper virus, as well as serology for *Neospora caninum* and *Toxoplasma gondii* were negative.

The clinical, MRI and CSF findings supported the clinical diagnosis of unilateral internal hydrocephalus with presumed periventricular encephalitis. Other inflammatory diseases of the brain such as meningoencephalitis of unknown origin (MUO) and concurrent unilateral congenital hydrocephalus causing the periventricular hyperintensities were also a possibility, although the young age of the patient was not typical for MUO. Bacterial or viral meningoencephalitis could not be completely ruled out but were considered much less likely. The hyperintensities present in the piriform lobes were thought to be post-ictal.

The dog was treated with phenobarbitone (3.4mg/kg BID PO) and corticosteroids (prednisolone, 1.1mg/kg SID PO). A quick clinical improvement was noted with no more seizures/ twitching. The patient continued to recover and was discharged four days after initial presentation.

Re-examination at the referring veterinarian was performed two weeks after the initial diagnosis. The patient appeared clinically well with no reported neurological signs. Blood work was performed and hematology revealed mild leukocytosis (20.6 x 10^9/L, reference 6-15) with normal biochemistry. Phenobarbitone serum concentration was also measured and was below the recommended therapeutic range (53 µmol/l, therapeutic range 65-194), but as the patient had not experienced any more seizure activity, the dose was not increased any further. The prednisolone dose was reduced after six weeks by 20%, and gradually the dose was reduced to the minimum that could control the clinical signs (0.5mg/kg SID). Nine months after the initial diagnosis, the patient remained stable on phenobarbitone (3mg/kg BID) and prednisolone (0.5mg/kg SID). The owners reported a low frequency of focal seizures, which was managed by increasing the phenobarbitone dose.

DISCUSSION

In this report, the authors describe the clinical signs, MRI and CSF findings, and medical management of a four-month-old English bulldog with unilateral hydrocephalus and presumed periventricular encephalitis. Unilateral hydrocephalus in dogs has not been previously reported in the veterinary literature. The MRI findings of periventricular encephalitis (although well described as a pathological disease) have not been described. Computerized tomography (CT) images of a single case with hydrocephalus and periventricular encephalitis have been described by Dewey (2002), but since then, there have been no other imaging reports on this disease.

Hydrocephalus and periventricular encephalitis affect juvenile dogs between two and six months old. No breed predisposition has been reported. The clinical signs mainly include forebrain signs and have an acute onset (Cantile et al., 1997). An infectious agent (bacterial or viral) has been hypothesized as the underlying cause of this condition. However, this has not been identified or reliably isolated. The etiology of the disease remains unknown (Wouda et al., 1981; Dewey, 2002). The patient of the present case did not show any cytological evidence of bacterial infection in the CSF. Therefore, no antibiotics were part of the treatment. The successful medical management with corticosteroids may imply an immune-mediated underlying cause, but this cannot be concluded based on this case alone.

With the exception of one case, which was diagnosed on CT images and CSF analysis (Dewey, 2002), in all the other reported cases, the diagnosis was based on gross and histopathological examination at necropsy. The diagnosis of periventricular encephalitis in the present patient was presumptive as it was based on clinical presentation, MRI and CSF findings. This reflects the clinical difficulties to reach definitive diagnosis in surviving patients with diseases of the central nervous system.

Hydrocephalus with associated skull enlargement can also be seen in the congenital form, which is the most common type of hydrocephalus in young dogs. However, the periventricular T2W SE and FLAIR hyperintensities with moderate contrast enhancement are more suggestive of an inflammatory process. Skull enlargement is a consistent finding in previously reported cases of hydrocephalus and periventricular encephalitis (Higgins et al., 1977; Wouda et al., 1981). The changes noted in the piriform lobes were most likely post-ictal given the history of focal seizures (Mellema et al., 1999).

The CSF analysis supported the imaging findings of an inflammatory process, and common infectious diseases were ruled out. Inflammatory changes have not been produced in experimental obstructive hydrocephalus in dogs, which leads to the hypothesis that the inflammation is the cause of it rather than the result (Weller et al., 1971). Mixed mononuclear pleocytosis can be seen in other types of meningoencephalitis (infectious, MUO) in dogs but the patient of the present case was tested negative for Toxoplasma, Neospora and distemper virus, and the young age (<6 month) and MRI lesion distribution render MUO unlikely.

A bacterial involvement in hydrocephalus and periventricular encephalitis has been suspected in previous reports (Higgins et al., 1977; Dewey, 2002). The only reported clinical case that survived this condition had a positive CSF culture and *Staphylococcus capitis* was isolated (Dewey, 2002). In other two reported cases, post-mortem bacteriological cultures isolated *Pasteurella multocida* and *Staphylococcus aureus* but were considered of questionable significance due to the high risk of contamination (Higgins et al., 1977; Wouda et al., 1981). In the case reported here, the CSF was not cultured and a bacterial infection could not be completely ruled out. However, the CSF cytology was not supportive of a bacterial infection. Additionally, the successful outcome of the patient without antibiotic therapy rendered a bacterial involvement highly unlikely.

The unilateral hydrocephalus in this dog is atypical as it has not been previously reported with this condition, neither with other causes of hydrocephalus, which is usually bilateral. Asymmetry of the lateral ventricles has been described; however it was in healthy dogs and dogs with idiopathic epilepsy and with no other changes in the MRI studies (Pivetta et al., 2013). The neurological deficits of the case presented here were mainly arising from the left forebrain rendering the imaging findings of the left hemisphere clinically relevant. Furthermore, a previous report

comparing the MRI findings in dogs with asymptomatic ventriculomegaly and dogs with symptomatic hydrocephalus also supported the authors' presumptive diagnosis of hydrocephalus (Laubner et al., 2015). The changes found in the symptomatic hydrocephalic cases share similarities with the case presented here, with a high ventricle/brain (>0.6), signs of periventricular edema, thinning of the ipsilateral cortical sulci, elevation of the corpus callosum and dorsoventral flattening of the interthalamic adhesion.

The pathophysiology of the unilateral hydrocephalus in this patient cannot be confirmed without histopathological examination, but a few theories have been confirmed. The normal CSF flow is directed from the lateral ventricles through the interventricular foramen to the third and fourth ventricles and the central canal (DeLahunta and Glass, 2009; Przyborowska et al., 2013). An obstruction at the level of the interventricular foramen can lead to unilateral hydrocephalus and this is a plausible assumption for this patient. The inflammatory process can lead to excessive release of exudative substances and tissue debris into the CSF, which can obstruct the foramen, but also create adhesions that interfere with its normal development, and subsequently lead to stenosis or complete obliteration (Higgins et al., 1977).

With regards to treatment of hydrocephalus, the aim is to reduce the CSF volume either by reduction of CSF production or by facilitating drainage. Medical management involves the use of corticosteroids or diuretics that can reduce CSF production. Although some dogs respond to medical treatment long-term, usually it provides only temporary improvement of clinical signs. Surgical treatment typically involves the placement of a ventriculoperitoneal shunt, which facilitates the drainage of CSF. The complication rate after surgical intervention can be as high as 29 % with most common complications involving shunt malfunctions due to obstructions, shunt infections, postoperative pain and seizures (Shihab et al., 2011; Biel et al., 2013; Giacinti, 2016). In the present case, the placement of a ventriculoperitoneal shunt was discussed with the owners of the patient but given the successful medical management and presence of a concurrent meningoencephalitis, it was not performed.

To conclude, this is the first report of unilateral hydrocephalus and presumed periventricular encephalitis in a juvenile dog with MRI imaging and successful outcome. Clinicians should consider this condition as a differential diagnosis for hydrocephalus, especially where there are periventricular T2W and FLAIR hyperintensities and contrast enhancement.

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