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CASE REPORT

Clinical and MRI findings of a suspected cortical malformation presented as a giant cerebral pseudomass in a German Shepherd dog

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Abstract

A 5-month-old German Shepherd dog was presented with cluster seizures. MR imaging showed a large irregular pseudomass in the central region of the cranial cavity, compatible with a malformation of cortical development. Despite the extensive changes, the patient was neurologically normal interictally 1 year following diagnosis.

KEYWORDS

brain development, canine, cortical malformation, heterotopia

1 | INTRODUCTION

Malformations of cortical development (MCDs) are a rare and heterogenous group of disorders of disrupted cerebral cortex formation. They can result from defects that involve either of the three major stages of cortical development including neurogenesis, neuronal migration and post-migrational development.[1] Although rare, the most reported cortical malformations in dogs and cats include hydranencephaly/porencephaly, polymicrogyria, and lissencephaly.[2–8] New types of MCD have been recently added to the veterinary literature, but a classification scheme (as described in humans) has not yet been established.[1,9–12] Intractable epilepsy and cognitive delay are the main clinical signs in humans with MCD, particularly when the affected area is large.[13] This case report describes the clinical and MRI findings, treatment and short-term outcome of a bizarre and dramatic suspected cortical malformation in a dog.

2 | CASE DESCRIPTION

2.1 | Clinical findings

A 5-month-old male German Shepherd dog weighing 16.8 kg was presented to the Small Animal Hospital of the University of Glasgow for further assessment of cluster epileptic seizures. The seizures started 24 h prior to presentation and were characterized by focal twitching of the ears

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and hypersalivation, progressing into generalized tonic–clonic seizures. The dog displayed five seizures before arrival, all lasting 30–60 s with no evident post-ictal phase. There were no previous health concerns. The puppy was quiet, alert, and responsive on admission. General physical examination demonstrated an asymmetry of the temporal bones on palpation of the head, with the right side slightly depressed compared to the left. Neurological examination showed a normal mentation and mild generalized proprioceptive ataxia. Postural reaction deficits were present in the left thoracic and left pelvic limbs. The segmental spinal reflexes were normal. Cranial nerve examination revealed a bilateral reduced menace response, more marked on the left side. The rest of the neurological examination was normal. Clinical findings were compatible with a forebrain lesion lateralised to the right.

Complete blood count and serum biochemistry profile were within normal limits apart from marginally increased AST (43 U/L, reference interval [RI] = 0–40 U/L), mildly increased creatinine kinase activity (646 U/L, RI = 0–150 U/L) and mildly decreased globulins (25 g/L, RI = 28–42). The results of the cerebrospinal fluid (CSF) analysis collected at the cerebellomedullary cistern showed mild albuminocytologic dissociation (total nucleated cell count: 0 cells/μL, RI < 5 cells/μL; protein concentration 40 mg/dL, RI < 25 mg/dL).

2.2 | MRI findings

Magnetic resonance (MR) images of the brain were acquired using a 1.5 Tesla scanner (Siemens Magnetom Essenza; Siemens Healthcare Ltd, Sir William Siemens Square, Frimley, Camberley, Surrey). The protocol included sagittal and dorsal T2-weighted images (3.5 mm slice thickness), dorsal T2-weighted CISS images (0.8 mm slice thickness), and transverse T1-weighted, T2-weighted, FLAIR and T2* images (4 mm slice thickness). MRI of the brain showed the striking absence of a normal cerebral cortex in the right parietal and occipital lobes resulting in large fluid-filled spaces, which appear continuous with the subarachnoid space (Figure 1). An irregular 4.5 cm × 3.9 cm × 2.9 cm pseudomass was present in the central region of the cranial cavity, extending across midline from the right side into a markedly dilated left lateral ventricle. This pseudomass showed an appearance similar to the cerebral cortex with layered areas of tissue isointense to gray and white matter on T2-weighted images. The rostrolateral aspect of this pseudomass was confluent with the cortex of the right frontal lobe and some small pockets of CSF were present in the lateral margin of the mass. The pseudomass was dorsal to the interthalamic adhesion, which was compressed on sagittal images and no septum pellucidum or corpus callosum was identified. Mild edema was present in the lateral aspect of the mass. The brainstem and cerebellum were unremarkable. There was expansion of the right occipital area of the calvarium with some thinning of the overlying bone associated with the subarachnoid fluid collection in this area (Figure 1). The changes were consistent with descriptions of gray matter heterotopia, with the midline displacement of the abnormal gray matter giving a "brain-in-brain" appearance.

2.3 | Treatment and short-term outcome

The dog was admitted to the hospital's intensive care unit and stabilized with a loading dose of levetiracetam (60 mg/kg IV once). Thereafter the dog was continued with a maintenance dose of levetiracetam, 30 mg/kg PO q8h. He also received prednisolone, 0.5 mg/kg PO q24h and omeprazole, 1 mg/kg q12h. Due to ongoing seizure activity the following day, the dog was administered a loading dose of phenobarbital (12 mg/kg/day IV) followed by a maintenance dose of phenobarbital 3.2 mg/kg q12h. The dog was discharged 24 h later with no further seizure activity. At the time of discharge, neurological examination showed moderate generalized proprioceptive ataxia with normal postural reactions and a normal menace response bilaterally.

At home, the dog continued to do well and showed no further seizures for 3 months. The prednisolone was gradually tapered down and stopped over 6 weeks. The dog returned to our hospital 4 and 10 months after discharge for management of cluster seizures. During his first revisit, blood was collected for measuring serum phenobarbital concentrations and results were within the mid-therapeutic range (112 μmol/L, RI = 65–170 μmol/L). He received a loading dose of potassium bromide (104 mg/kg PO q24h for two consecutive days) followed by a maintenance dose of 40 mg/kg PO q24h. The dosages of phenobarbital and levetiracetam were both increased to 4.8 mg/kg PO q12h and 30 mg/kg PO q8h, respectively. He returned once more for treatment of cluster seizures 6 months later. The dog had grown, and the medication had not been adjusted to his increased weight. Serum phenobarbital and bromide concentrations measured during this visit were 92 μmol/L and 1.41 mg/mL (bromide RI = 0.8–2.0 mg/mL) respectively. After the dose increase, the dosages were equal to the dosages prescribed during his previous visit (phenobarbital 4.8 mg/kg PO q12h, bromide 30 mg/kg PO q24h and levetiracetam 20 mg/kg q8h). At the time of writing, 14 months after diagnosis, the dog was doing well with occasional seizure activity. Repeated normal neurological examination at re-examination.

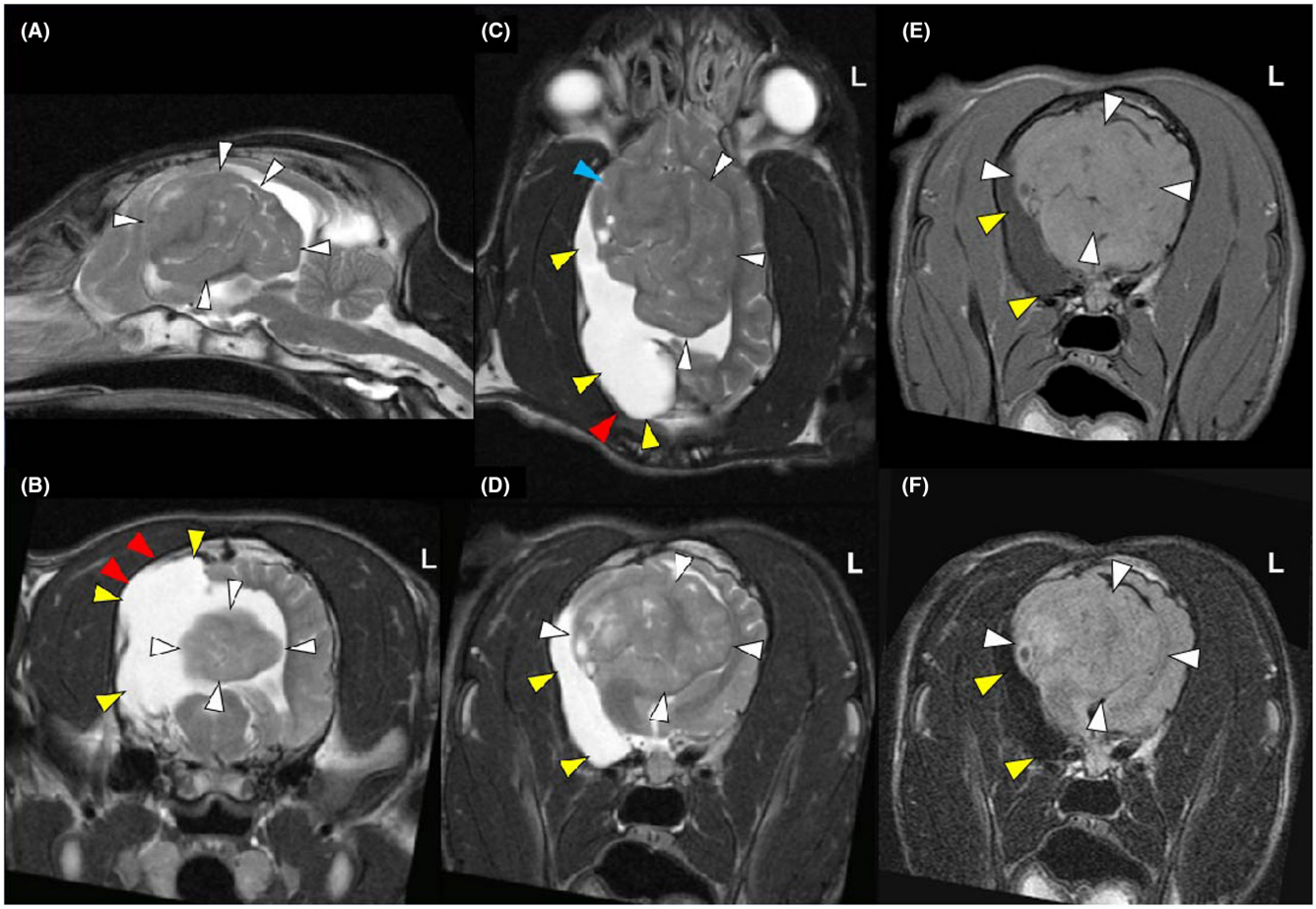

FIGURE 1 MRI images of the brain showing T2-weighted sagittal (A), dorsal (C) and transverse images of the occipital (B) and thalamic region (D), and T1-weighted (E) and FLAIR (F) transverse images of the thalamic region of the brain. A large pseudomass (white arrowheads) with a similar signal to white and gray matter and which is confluent with the right frontal cortex (blue arrowhead) projects across the midline and into the dilated left lateral ventricle. There is a large fluid-filled space that appears continuous with the right subarachnoid space (yellow arrowheads) with thinning of the right occipital bone (red arrowheads) and an absence of normal right parietal and occipital cerebral structures.

3 | DISCUSSION

Our case describes a giant suspected cortical malformation in a dog, replacing most of the right cerebral hemisphere and affection of the overlying bone. MCDs are believed to derive from a disruption of three major stages of cortical development including cell proliferation and apoptosis, cell migration and post-migrational development.[1] In humans, migration of neurons starts around the 5–6 gestational week and ends around the 30–35 gestational weeks.[1] Neurons start migrating from the ventricular and subependymal zones after completing their final division and having established their polarity. Migration occurs either radially or, less commonly, tangentially. Too early or too late migration leads to disruption of the normal neural migration and associated disorders.[1] A disorder in neuronal migration was suspected in this case. The parenchyma of the mass had similar MR sequence characteristics to the normal cerebral cortex, however present in an abnormal location. It included a mixture of white and gray matter and involved more than one lobe and overlying cortex. Histopathology would be required to confirm the diagnosis; however, this was not available in our case due to the fair clinical progress following medical treatment. Although less compatible with the MRI findings, other MCDs such as, for example, a neural hamartoma (which is an excess growth of normal cells and tissue native to the organ[14]) of the cerebral cortex, could not be completely excluded.

Cortical malformations have previously been described in dogs and cats but as these conditions are rare, there is no clear classification scheme.[2] Several classification schemes for MCD have been developed in humans and this process is dynamic and constantly evolving over time as knowledge is gained about underlying pathological mechanisms.[1] The definitive diagnosis of MCD in the medical literature is based on neuropathological findings. Practically, a subclassification is made

with neuroimaging findings, associated clinical phenotyping and genetic findings as pathological tissue is rarely available.[1] A recently published consensus document describes a practical approach for the imaging diagnostic appearance of MCD in humans.[1,15] To clarify, neuronal heterotopia is defined as a cluster of normal neurons in an abnormal location. According to the most recent scheme, gray matter heterotopia is classified as a subgroup of MCD and involves clusters of normal neurons in abnormal locations, mainly due to abnormal neuronal migration.[15] They can be seen on MRI as conglomerates of gray matter in heterotopic locations which are isointense with the cerebral cortex on all MR pulse sequences and are categorized based on morphology and location.[16] Gray matter heterotopia can be further subdivided in periventricular nodular heterotopia and subcortical (non-band) heterotopia. Midline brain-in-brain malformation is a subtype of subcortical heterotopia and is characterized by a bizarre mixture of gray and white matter which have been described as variations of holoprosencephaly.[1] This is an extremely rare condition in humans and to date, only four cases have been reported. All cases included a cortical midline mass and an abnormal or absent corpus callosum,[17] identical to our case.

A classification scheme for MCD does not exist in veterinary medicine. There are several single case reports in veterinary medicine describing neuronal heterotopia including heterotopia in a miniature schnauzer, a sea lion, a cat and a chihuahua.[9–12] The three latter reports describe MRI findings compatible with gray matter heterotopia, which was confirmed with histopathology: two subcortical heterotopia and one periventricular heterotopia, respectively.

Based on the MRI findings, our case shows similarities with giant subcortical heterotopia, more specifically, midline brain-in-brain malformation. Both include a huge subcortical mass, isointense to the gray matter, absence of the corpus callosum, and an abnormal overlying cortex. 'Giant' has been reserved for cases of subcortical heterotopia with unilateral diffuse and extensive heterotopia involving more than one lobe and the overlying cortex.[13] It must be emphasized that causes for poor differentiation of the forebrain are multiple and diverse resulting in various phenotypes that, despite elaborate classification schemes, often cannot be simply classified.[13] Subcortical heterotopia, for example, has a broad imaging spectrum which does not completely cover its anatomical terminology as it is not limited to only gray matter and may also involve abnormal migration of white matter.[1] This also accounts for the classification of midline brain-in-brain malformation as the pathogenesis remains unclear and might be related to an original defect compromising both process of hemispheric cleavage and cortical development.[17]

Malformations of cortical development in people show a high incidence of neurological deficits, such as epilepsy and mental retardation.[18] Drug-resistant epilepsy and subsequent progressive clinical deterioration is particularly a concern in cases with giant subcortical heterotopia. Complete surgical excision of subcortical heterotopia has been associated with a favorable outcome and may result in seizure-freedom.[13] Seizures in cases with MCD have also been described in veterinary medicine as the malformation forms an epileptogenic lesion.[19] Clinical signs related to intracranial malformations in previous veterinary cases varied from seizures only to progressive neurological deficits.[10,11] A large surface area was affected in our dog, and it was hypothesized that the dog would respond poorly to medical management. However, despite the extent of the lesion, repeated interictal neurological examination was normal with no postural reactions or menace response deficits as seen on initial presentation. At home, the owners did not notice any behavioral or cognitive impairment, more than 1 year following the MRI scan. This is important information as the history of cluster seizures and extent of the lesion could warrant a poor prognosis and therefore many owners could have opted for euthanasia. Although the dog was receiving three antiepileptic drugs at the time of writing, the seizures were relatively well-controlled, and the dog was showing cluster seizures only every 3–4 months. The prognosis may be similar to other forms of idiopathic epilepsy, but we would require information on the long-term follow up on our case to be able to confirm this.[20] An important factor with regards to seizure management in our case, was the dog's fast-growing body weight which resulted in underdosing. The dog's seizures may have been better controlled should the medication have been altered more frequently according to the change in body weight.

In summary, cortical malformations in dogs and cats are rare but new types have started to be identified recently, resembling their human counterpart. They should be considered as a rare differential diagnosis in young dogs presented with seizures. Although further specification, given the lack of histopathology, was not possible in our case, this is the first report that describes a dog with MRI findings of a suspected MCD presenting as a giant cerebral pseudomass. Despite the extensive changes, our case was neurologically normal interictally with seizures as the only clinical manifestation, which were fairly controlled with multidrug treatment. Future research might be of interest regarding this type of malformation, such as investigating the pathogenesis, a possible genetic background and the feasibility of surgical excision of the mass as a treatment option.

AUTHOR CONTRIBUTIONS

Jos Bongers: Conceptualization; writing – original draft; writing – review and editing. **Rodrigo Gutierrez-Quintana:** Supervision; writing – original draft; writing – review and editing. **Gawain Hammond:** Conceptualization; writing – original draft; writing – review and editing. **Roberto José-López:** Supervision; writing – original draft; writing – review and editing.

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The authors disclose no conflict of interest.

DATA AVAILABILITY STATEMENT

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CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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