MRI Diagnosis of Suspected Subcortical Heterotopia in a Mixed-Breed Dog with History of Seizures

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ABSTRACT

A rare case of congenital brain anomaly in a 2-year-old mixed-breed neutered female dog is presented in this study. The dog was admitted for further diagnosis because of episodic tonic-clonic generalised seizures. All blood tests and urinalysis results were unremarkable. MRI of the brain revealed an increase in volume of the frontal lobe, which was isointense to the grey matter and non-contrast enhancing and consistent with congenital subcortical heterotopia.

Keywords: Dog, Seizure, Subcortical heteropia, MRI diagnosis

INTRODUCTION

Some congenital defects are inherited from the parents, while others are caused by environmental factors in the uterus, such as nutritional deficiencies or some viral infections. For many of them, the cause is unknown. Puppies are born with a nervous system that is not fully developed, and birth defects may not become apparent until they begin to walk. In some cases, evidence of an inherited disorder may not be seen until the dog has reached adulthood, even though the defect has been present since birth. Congenital anomalies of the nervous system are categorized according to the primary region affected: forebrain, cerebellum, brain stem, spinal cord, peripheral nerve, or multifocal disorders that include signs of disorder of more than one area.Grey matter heterotopias describe a group of migration disorders in which neuronal cells fail to migrate normally during the development of the cerebral cortex. Gray matter heterotopias can be subdivided into 3 groups: subcortical heterotopias are nodular or curvilinear masses of gray matter, which protrude into the white matter while being connected to the overlying cerebral cortex, band heterotopias also named double cortex are layers of gray matter that lack any connection to the cortex, and periventricular nodular heterotopias, when nodules of gray matter are found unilaterally or bilaterally in a proximity to the lateral ventricles, protruding into the lumen or lining the ventricular walls. These lesions were described to be epileptogenic not only in humans, but there were also a few clinical case reports in dogs and cats (Barkovich 2000, Cooper *et al*. 2015, Herkommer *et al*. 2020, Cocchetto *et al*. 2022, and Bongers *et al*. 2023).

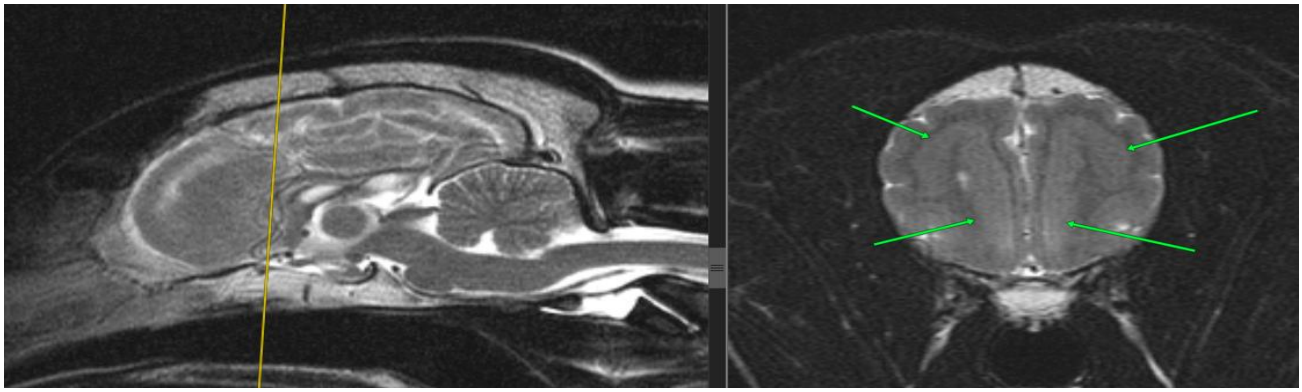
CASE HISTORY AND OBSERVATION

A 2-year-old mixed-breed intact female dog with a history of tonic-clonic seizures was presented to the clinic. The first clinical signs appeared two weeks ago; since that time, it has had seven seizures. At admission, the dog was bright, alert and responsive, with no signs of mental state changes and ataxia. The dog was normothermic, normopneuic, with no signs of any health issues. The cranial nerves reflexes, spinal reflexes a postural

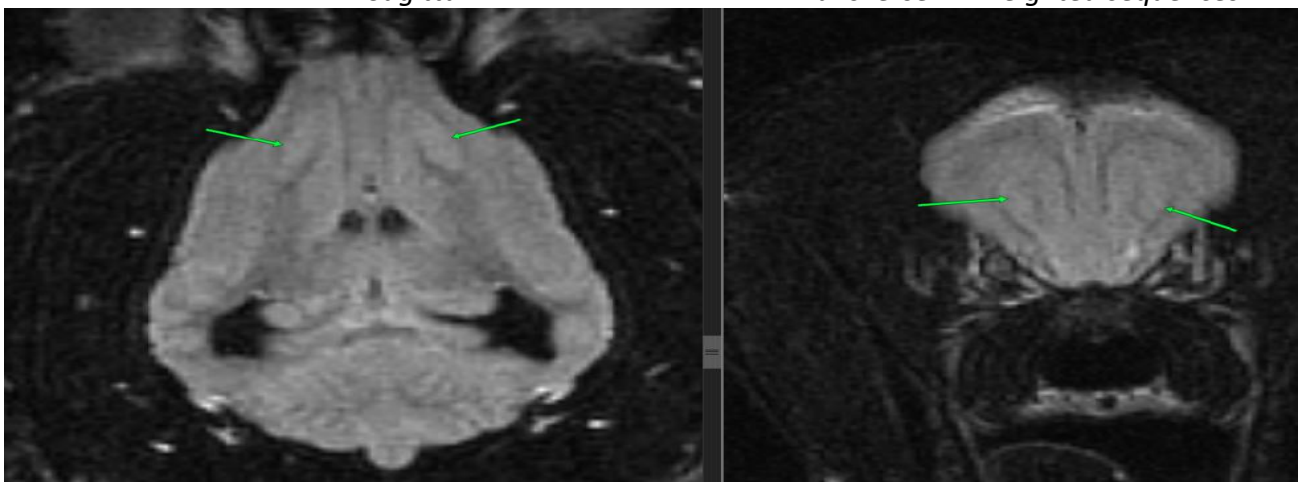
reflexes were all normal. The venous blood samples and samples from the urine were unremarkable and within normal limits, as well as no pathological changes were found on thoracic x-ray images and abdominal ultrasound. Cerebrospinal fluid samples were within normal limits. To exclude congenital and acquired pathology of the brain, magnetic resonance imaging was performed, which revealed signs of possible subcortical heterotopia. This finding was highly suspected to be the cause of seizures in this case. There is a visible increase in volume of the frontal lobe in all of these images, which is isointense and non-contrast enhancing, suggesting subcortical heterotopia in the frontal lobe region (arrows).

TREATMENT AND DISCUSSION

Malformations of cortical development are a heterogeneous group of lesions often associated with drug-resistant epilepsy in human medicine. There is a lack of information regarding this diagnosis in veterinary medical literature. This paper aimed to describe the clinical presentation and imaging findings in a young adult dog with a suspected malformation of cortical development presented with a history of severe generalised seizures that did not improve despite initiation of antiepileptic therapy. The dog was humanely euthanised a few days after investigation at the owner's request due to continuing seizures while being orally administered a combination of antiepileptic drugs (phenobarbital 3mg/kg bid, levetiracetam 20mg/kg tid). The owner declined histopathological examination.



A. Sagittal *B. Transverse T2-weighted sequences*



C. Dorsal *D. Transverse FLAIR sequence*

Images from the magnetic resonance obtained with 1.5 Tesla Siemens, 3.0 mm slices

In human medicine, grey matter heterotopias (GMH) are neurodevelopmental disorders associated with abnormal cortical function and epilepsy. Subcortical band heterotopia (SBH) and periventricular nodular heterotopia (PVNH) are two well-recognised GMH subtypes in which neurons are misplaced, either forming nodules lining the ventricles in PVNH or forming bands in the white matter in SBH. Although both PVNH and SBH are commonly associated with epilepsy, it is unclear whether these two GMH subtypes differ in terms of pathological consequences or, on the contrary, share common altered mechanisms. The work of Vermoyal *et al*. (2024) supports that GMH represent a complex set of disorders, associating both shared and diverging pathological consequences, and contributing to forming epileptogenic networks with specific properties. A deeper understanding of these properties may help to refine current GMH classification schemes by identifying morpho-electric signatures of GMH subtypes, to potentially inform new treatment strategies (Vermoyal *loc cit*.).

There are a few case studies, including a study by Herkommer (*loc cit.*), which described a case of a female Chihuahua puppy examined for a history of epileptic seizures and abnormalities in gait and behaviour. Results of the clinical examination were consistent with multifocal neurological dysfunction with localization in the forebrain and spinovestibular system. Magnetic resonance imaging showed multiple bilateral periventricular nodules, isointense to grey matter and ventriculomegaly. Histopathological and immunohistological examination of the brain revealed periventricular nodules consisted of neurons, fewer astrocytes, and some oligodendroglia. These findings were consistent with periventricular nodular heterotopias. Rusbridge and Wilkins (2002) described one of the first litters of Lagotto Romagnolo dogs bred in England that had locomotion difficulties. The most severely affected pup was euthanized and the brain was examined. The dog had prognathia and a brachycephalic skull, atypical for the breed. Although the brain was macroscopically unremarkable, histology showed a neuronal migration disorder characterized by heterotopia of the cortex, cerebellum, and pons.

Malformations of cortical development 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. In humans, migration of neurons starts around the 5–6 gestational week and ends around the 30–35 gestational weeks. 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. A disorder in neuronal migration was suspected in a case described by Bongers *et al*. (*loc cit*.). The parenchyma of the mass found in the brain of a German Shepherd puppy had similar MRI sequence characteristics to the normal cerebral cortex; however, present in an abnormal location. It included a mixture of white and grey matter and involved more than one lobe and overlying cortex. Histopathology would be required to confirm the diagnosis; however, this was not available in this case due to the fair clinical progress following medical antiepileptic treatment.

This disease of neuronal heterotopia was described in a few other animal species, including the cat. A domestic shorthair kitten was presented for evaluation and further treatment of seizures in a study by De Jesus

et al. (2018). Magnetic resonance imaging of the brain revealed a large multilobulated mass in the third ventricle extending into the right lateral ventricle with secondary obstructive hydrocephalus. The mass was homogeneously isointense to grey matter on T2W, T2-FLAIR, T2*W, T1W, and ADC images, and hyperintense on DW-EPI. There was no appreciable contrast enhancement. Seizures were managed medically and with subsequent ventriculoperitoneal shunt placement. Clinical status later deteriorated, and the cat was euthanized. Histopathology confirmed that the mass was a result of neuronal heterotopia. There is also information regarding a parvovirus-associated congenital ataxia in cats where the uniform granular layer atrophy is accompanied by Purkinje cells heterotopia and where the pontine nuclei are preserved (Summers *et al*., 1995).

SUMMARY

In summary, we can assume that congenital nervous system abnormalities such as cortical heterotopia, although an unusual diagnosis, should be considered as a potential differential diagnosis in young adult canine patients with a history of generalised seizures. Based on the available literature, the overall prognosis is questionable.

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