



NOTE

Internal Medicine

Lissencephaly in a Pekingese

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ABSTRACT. A 1-year-old neutered male Pekingese was presented for evaluation and further treatment of cluster seizures. The dog had behavioral abnormalities, and a prosencephalic lesion was suspected following neurological examination. The dog showed signs of learning difficulty. Magnetic resonance imaging of the brain revealed a remarkably smooth cerebral cortex with a reduced number of gyri, as well as a cystic lesion associated with the quadrigeminal cistern. A diagnosis of lissencephaly, concurrent with a quadrigeminal cisternal cyst, was made. High-dose and multiple anticonvulsants were necessary to control the seizures. This is the first report of lissencephaly in a Pekingese.

KEY WORDS: lissencephaly, magnetic resonance imaging, Pekingese

Lissencephaly is a congenital malformation of the brain, characterized by a smooth-appearing cerebrum with a reduced number or absence of gyri and sulci, a thickened cerebral cortex, and the loss of the normal microscopic laminar pattern of neurons [8, 9]. Histologically, a normal cerebral cortex has 6 distinct neuronal layers. During brain development, the earliest-born neurons migrate from the deepest layer to an appropriate area within the cortex. Later-born neurons migrate past the earlier-born neurons, and thus the final laminar cortical layers are formed ‘inside-out’ [6, 16]. An arrest of, or defect, in neuronal migration results in cortical layer malformations, and lissencephaly is the severe form of this disorder [13, 16].

In humans, lissencephaly has been found to be linked to mutations in several genes that have roles in neuronal migration [3, 4, 12]. In veterinary medicine, lissencephaly is an uncommon condition, with only a small number of cases reported in the literature as an isolated disorder [7, 10, 14, 19, 21]. Among those cases, Lhasa Apso appears to be overrepresented [10, 19, 21]. Therefore, it is assumed that lissencephaly in dogs may result from a genetic abnormality; however no such abnormality has yet been identified. Reported clinical signs in dogs include seizures, behavioral abnormalities such as episodic depression, confusion, and aggression, visual deficits, and learning difficulties.

The present report describes the clinical findings and magnetic resonance imaging (MRI) characteristics of lissencephaly in a Pekingese.

A 1-year old neutered male Pekingese was presented to a primary care veterinarian with a 2-day history of cluster seizures. Complete blood count and serum biochemistry findings were unremarkable. Although treatment with zonisamide (5 mg/kg PO q12h, Consave, DS Pharma Animal Health, Osaka, Japan) was commenced at the time of initial presentation, another seizure episode occurred the following week. The seizures were described as generalized tonic-clonic type with hypersalivation. The dog was referred to the Veterinary Medical Center-Obihiro University of Agriculture and Veterinary Medicine (VMC-OUAVM) for further evaluation.

At the time of presentation to VMC-OUAVM, the dog was restless and highly aware (i.e. repeatedly looking around). The gait was normal. On neurological examination, postural reactions were decreased in the forelimbs and spinal reflexes were mildly exaggerated in all four limbs. Pain was not elicited during cervical, thoracic, or lumbar spinal palpation. Pupillary light reflexes were normal, but the menace responses were absent bilaterally. The dog’s eyes and head did not follow cotton balls dropped in front of each eye. The remainder of the neurological examination was within the normal limit. Neuroanatomic localization of the lesion was generalized to the prosencephalon. Further inquiry revealed that the owner had difficulty in managing house-training.

Results of complete blood counts and serum biochemistry were unremarkable, except for mild elevation in alanine aminotransferase (109 IU/l; reference range 10–100 IU/l). Skull, cervical, thoracic, and abdominal radiographs did not detect any abnormalities.

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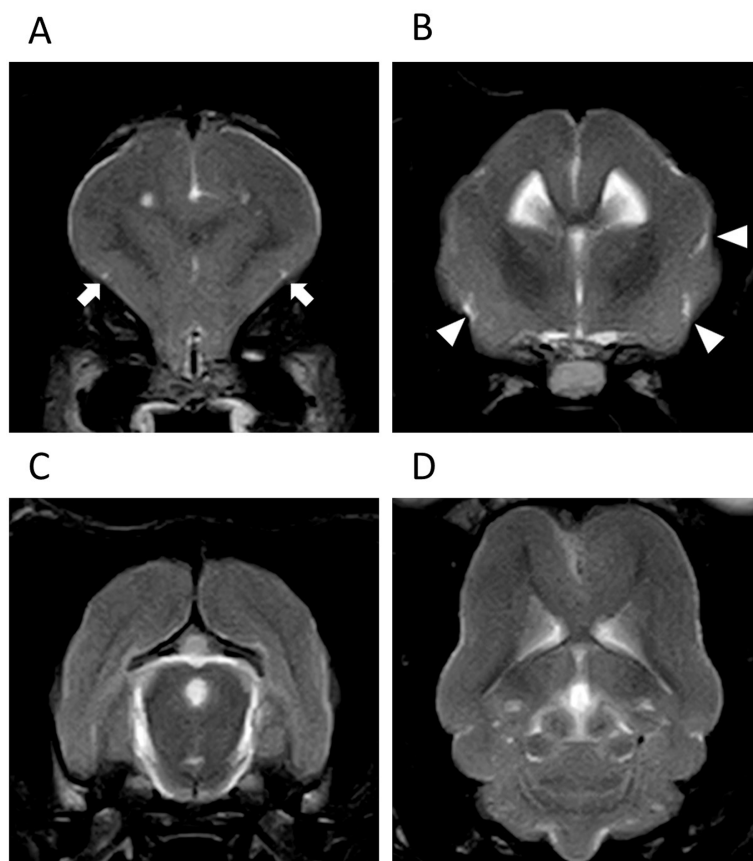


Fig. 1. Transverse T2WI at the level of the frontal lobes (A), the mid-diencephalon (B), and the midbrain (C) and dorsal T2WI at the level of corpus callosum (D) showing a remarkably smooth cerebral cortex. A small number of shallow sulci were present in the frontal (arrows) and temporal lobes (arrowheads), but absent in the occipital lobes.

Brain MRI was performed using a 0.4-Tesla open magnet (APERTO lucent, Hitachi Medical Systems, Tokyo, Japan). Anesthesia was induced by slow intravenous administration of propofol (10 mg/kg IV, PropoFlo28, DS Pharma Animal Health, Osaka, Japan) and maintained with an isoflurane and 100% oxygen mixture. Transverse T1-weighted images (T1WI) (TR=320 ms, TE=12 ms, FOV=150 mm, 3.5 mm thick/0.4 mm gap), T2-weighted images (T2WI) (TR=3,889 ms, TE=100 ms, FOV=150 mm, 3.5 mm thick/0.4 mm gap), fluid attenuated inversion recovery images (TR=8,385 ms, TE=90 ms, TI=2,000 ms, FOV=150 mm, 3.5 mm thick/0.4 mm gap), T2*-weighted images (TR=500 ms, TE=22 ms, flip angle 30°, FOV=150 mm, 3.5 mm thick/ 0.4 mm gap), sagittal T1WI (TR=320 ms, TE=12 ms, FOV=200 mm, 2.5 mm thick/0.5 mm gap) and T2WI (TR=3,662 ms, TE=109 ms, FOV=200 mm, 2.5 mm thick/0.5 mm gap), dorsal T2WI (TR=3,889 ms, TE=100 ms, FOV=150 mm, 3.5 mm thick/0.4 mm gap), and post-contrast [Gadoteridol (0.1 mmol/kg IV, ProHance, Eisai, Tokyo, Japan)] transverse and sagittal T1WI were acquired.

MRI revealed that the surface of the cerebrum was remarkably smooth and the number of gyri on the entire cerebrum hemispheres were reduced or even absent at the midbrain level. The cortical grey matter was abnormally thick (Fig. 1). Additionally, there was a cystic lesion in the quadrigeminal cistern in association with the 3rd ventricle (Fig. 2). Parenchymal compression of the occipital lobes by the cystic lesion were identified. The percentage of occipital lobe compression, calculated by a method described previously [15], was 21%. The remainder of the brain structures appeared to be normal, and there was no evidence of contrast enhancement throughout the brain.

Cerebrospinal fluid collected from the cerebellomedullary cistern, immediately after MRI, showed no abnormalities.

Based on these findings, a diagnosis of lissencephaly was made, concurrent with a quadrigeminal cisternal cyst. An increased dose of zonisamide was instructed, and the dog was returned to the referring clinic for anticonvulsant therapy. The dog was treated with zonisamide (9.4 mg/kg PO q12h), potassium bromide (40 mg/kg PO q12h, Wako 1st Grade, Wako Pure Chemical Industries, Osaka, Japan), and diazepam (0.5 mg/kg PO q12h, Cercine, Takeda Pharmaceutical Co., Osaka, Japan). Three months following diagnosis, the referring veterinarian reported that there had been no cluster seizures and the frequency of seizures had reduced to approximately one per month.

In humans, lissencephaly is divided into classical lissencephaly (also known as type 1) and cobblestone cortical malformation (type 2). Classical lissencephaly is distinguished from cobblestone cortical malformation by the abnormally thick cortex and



Fig. 2. Transverse T2WI at the level of the rostral part of the midbrain (A), mid-sagittal brain T2WI (B) and T1WI (C). A cystic lesion at the quadrigeminal cistern in association with the 3rd ventricle was identified.

absence of other brain malformations, like microcephaly, agenesis of the corpus callosum, or cerebellar hypoplasia [8]. Based on the MRI findings, the present and previously described cases [7, 10, 14, 19, 21] are equivalent to classical lissencephaly in humans. Classical lissencephaly is further divided, based on imaging results, into 6 grades, from severe grade 1 (complete agyria) to mild grade 6 (subcortical band heterotopia only) [8]. The MRI results of the present case, showing diffuse agyria with a few shallow undulations over the frontal and temporal poles, were consistent with grade 2a. In humans, the severity of lissencephaly is thought to determine prognosis [2], however it is unclear whether the same is true for dogs given that only 1 case, classified as grade 2b, was previously applied to this grading system [7]. Nevertheless, dogs with lissencephaly appear to be well controlled by anticonvulsants and live a long life [7].

The clinical findings of the present case, such as the early onset of seizures, absence of the menace responses, behavioral abnormalities, and difficulty in house-training were consistent with those in previously reported cases [7, 10, 14, 19, 21]. Quadrigeminal cisternal cysts can also be the cause of early onset of seizures [5, 15, 20]. It has been reported that quadrigeminal cisternal cysts, that cause occipital lobe compression greater than 14%, are always associated with clinical signs [15]. In the present case, it could not be determined whether the seizures were caused by lissencephaly alone, because occipital lobe compression was 21%. Treatment options for quadrigeminal cisternal cysts include medical management and surgery [5, 15, 20]. In a previous case of a Lhasa apso with lissencephaly concurrent with quadrigeminal cisternal cyst, surgical fenestration of the cyst successfully reduced the seizure frequency and intensity, although the percentage of occipital lobe compression was not described [19]. In the present case, the seizures were successfully controlled by medical management, however, surgical intervention could reduce amount of anticonvulsants required.

Spinal reflexes were exaggerated in all four limbs in the present case. A 7-year-old mixed-breed dog with lissencephaly and an intracranial arachnoid cyst, concurrent with cervical intervertebral disc disease, was reported previously [14]. Although cervical MRI was not performed, it is unlikely that the present dog had cervical lesion-like intervertebral disc disease or cervical spinal arachnoid cysts because the dog was 1-year old and the cervical spinal cord, at the level of C1-5, was evaluated in the sagittal images of the brain. In addition, there was no evidence of compression of the brainstem by the quadrigeminal cisternal cyst. Therefore, the exaggerated spinal reflexes were assumed to be caused by lissencephaly. In fact, one dog in the previous report showed bilateral accentuation of the patella reflexes, although the remainder demonstrated normal spinal reflexes [10]. In humans, exaggerated tendon reflexes were reported to be one of the most common neurological findings in classical lissencephaly [17].

Classical lissencephaly in humans is caused by mutations of three genes: LIS1, DCX and TUBA1A [3, 4, 12]. Since Lhasa Apso appears to be overrepresented, lissencephaly in dogs is also considered to be a genetic disorder [10, 19, 21]. It has been revealed that three Asian companion breeds of similar appearance, Lhasa Apso, Shih Tzu, and Pekingese have close genetic relationship [11, 18]. Interestingly, there was another previously reported case of a mixed-breed dog similar to Pekingese [14]. Therefore, the present case, lissencephaly in a Pekingese, would be noteworthy. Although quadrigeminal cisternal cysts and lissencephaly have been diagnosed concurrently in both Lhasa Apso and Asian brachycephalic mixed-breed dogs, these were considered to be unrelated findings because of the different pathophysiologies of the 2 disorders [14, 19]. Previous studies have reported that male, brachycephalic, and small breed dogs are overrepresented among dogs with quadrigeminal cysts [5, 15, 20]. The 2 dogs described above, and the present dog, were all neutered males, brachycephalic, and small breed dogs.

In the present case, the diagnosis of lissencephaly was made based on MRI findings only, and lacking of the histopathological confirmation is a limitation. Until recently, reports of lissencephaly in dogs were based on postmortem findings [10, 21]. On the other hand, because MRI has become more readily available in veterinary medicine, antemortem diagnoses of lissencephaly have been made by imaging findings alone [7, 14, 19]. In fact, the diagnosis of lissencephaly is usually made by ultrasound, computed tomography, or MRI in humans [2, 13, 17]. However, previous studies have reported that diagnosis of the quadrigeminal cisternal

cysts in dogs should be based on histopathology [1, 15]. Supracollicular fluid accumulations might be more appropriate in the present case.

In conclusion, this is the first report of lissencephaly in a Pekingese. Considering the predisposition in the Lhasa Apso breed, and genetic relationship between Lhasa Apso and Pekingese, the assumption, that lissencephaly is a genetic disorder in dogs, is supported by the present case. Lissencephaly should be considered a rare differential diagnosis for Pekingese dogs with seizures.

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