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Abstract

Polymicrogyria and asymmetric dilation of the lateral ventricles were seen in related Standard poodles that had cortical blindness. Three of the affected dogs also had gait and postural abnormalities, and one of these had seizures. Two of the affected dogs were littermates. Thorough ophthalmologic and neurologic examinations (including electroretinography, electromyography, cerebrospinal fluid analysis, plain radiographs, and computerized tomography scans) revealed no significant abnormalities outside of the brain that would account for the blindness. Computerized tomography scans in three dogs demonstrated bilateral dilation of the lateral ventricles which was more severe in the right. All dogs were necropsied between 5 and 9 months of age and had strikingly similar brain abnormalities. Numerous small irregular gyri with shallow sulci covered the middle and caudal dorsal and lateral cerebral cortex. The bony ridges of the inner calvaria in this area conformed to the underlying microgyral pattern. The lateral ventricles were asymmetrically dilated with the right more severely affected, particularly in the occipital area, and the cortical grey and white matter, including the corpus callosum, were thinned in these areas. The third and fourth ventricles and mesencephalic aqueduct were normal. Histologically, there was thinning and simplification of the cortical grey matter with an increased density of medium to large neurons. The corona radiata and subcortical white matter were also thinner than normal with no evidence of demyelination or astrocytic scarring. This congenital anomaly of the visual cortex causing blindness in the Standard Poodle appears to be inherited as an autosomal recessive trait.

Disciplines

Medicine and Health Sciences | Veterinary Medicine | Veterinary Pathology and Pathobiology

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Polymicrogyria and asymmetric dilatation of the lateral ventricles were seen in related Standard Poodles that had cortical blindness. Three of the affected dogs also had gait and postural abnormalities, and one of these had seizures. Two of the affected dogs were littermates. Thorough ophthalmologic and neurologic examinations (including electroretinography, electromyography, cerebrospinal fluid analysis, plain radiographs, and computerized tomography scans) revealed no significant abnormalities outside of the brain that would account for the blindness. Computerized tomography scans in three dogs demonstrated bilateral dilatation of the lateral ventricles which was more severe in the right. All dogs were necropsied between 5 and 9 months of age and had strikingly similar brain abnormalities. Numerous small irregular gyri with shallow sulci covered the middle and caudal dorsal and lateral cerebral cortex. The bony ridges of the inner calvaria in this area conformed to the underlying microgyral pattern. The lateral ventricles were asymmetrically dilated with the right more severely affected, particularly in the occipital area, and the cortical grey and white matter, including the corpus callosum, were thinned in these areas. The third and fourth ventricles and mesencephalic aqueduct were normal. Histologically, there was thinning and simplification of the cortical grey matter with an increased density of medium to large neurons. The corona radiata and subcortical white matter were also thinner than normal with no evidence of demyelination or astrocytic scarring. This congenital anomaly of the visual cortex causing blindness in the Standard Poodle appears to be inherited as an autosomal recessive trait.

Introduction

Polymicrogyria is the presence of multiple small gyri in the cerebral cortex and is also referred to as microgyria. In humans, polymicrogyria/microgyria (multiple small malformed cerebral convolutions) is distinguished from polygyria (excessive superficial sulcation associated with hydrocephalus) based on histologic criteria.¹ We are not aware of any previous reports of polymicrogyria in the dog or in other small domestic animals. There are three reports of polymicrogyria in cattle; one in Hereford calves,² one in Murray grey calves,³ and one in calves of undisclosed breeds.⁴ The

undisclosed breeds in the earliest report⁴ involved the same group of cattle in Nebraska as the subsequent report in Hereford calves.¹ All appeared to be inherited as a simple autosomal recessive trait. In the Hereford calves there were also other anomalies observed including hydrocephalus, cerebellar hypoplasia and dysplasia, central myelin abnormalities, ocular defects, and muscular dystrophy.² Microgyria has also been reported as an uncommon manifestation of Akabane viral infection in sheep, although usually in association with other more typical lesions of that disease.⁵ There are also experimentally induced models of microgyria in the rat.^{6,7} Polymicrogyria/microgyria is frequently re-

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Blindness in Standard Poodles

TABLE 1
Signalment and Clinical Findings in Four Standard Poodles With Polymicrogyria

Case #	1	2	3	4
Sex	Male	Male	Male	Female
Age at onset of clinical signs	< 5 months	birth	< 5 weeks	< 5 weeks
Age at necropsy	7 months	5.5 months	5 months	9 months
Clinical signs	Blind	Blind Hypermetria Seizures	Blind Hypermetria	Blind Hypermetria
Ophthalmoscopy	Normal	Normal	Normal	Normal
ERG ^a	early PRA ^b	NE ^c	Normal	Normal
Neurologic exam	Normal PLR ^d Absent menace	Normal PLR Absent menace	Normal PLR Absent menace	Normal PLR Absent menace
CSF ^e exam	NE	Normal	Normal	Normal
EMG ^f	NE	NE	NE	Normal
CT ^g scan	NE	Asymmetric ventricular dilation	Asymmetric ventricular dilation	Asymmetric ventricular dilation ^h

^a ERG = electroretinography

^b PRA = progressive retinal atrophy

^c NE = not examined

^d PLR = pupillary light responses

^e CSF = cerebrospinal fluid

^f EMG = electromyography

^g CT = computerized tomography

^h confirmed by MRI

ported in humans^{1,8,9} and, although the pathogenesis is usually unknown, a few cases have been associated with fetal intoxications or cytomegalovirus infection.

This report describes the clinical and pathological findings in four Standard Poodles with polymicrogyria and ventricular dilation. Pedigree analysis of these dogs suggests an autosomal recessive mode of inheritance. Unlike previously reported cases of this condition in other species, the affected dogs had a consistent clinical phenotype, and the salient presenting sign was blindness.

Case Reports

The signalment and clinical findings are summarized in Table 1. All four dogs had similar clinical presentations, and all were referred to the Veterinary Hospital of the University of Pennsylvania (VHUP) for evaluation of blindness.

CASE 1

A male Standard Poodle was referred to VHUP at 6.5 months of age with a history of blindness that was noticed before 5 months of age. On neurologic examination, the pupillary light responses (PLR) were normal, but no menace response could be elicited. In bright or dim light, the dog frequently bumped into stationary objects but was otherwise normal. Ophthalmologic examination revealed no abnormalities. Electroretinography

(ERG) testing performed under general anesthesia demonstrated early abnormalities in rod function but normal cone function. These abnormalities are characteristic of early stages of progressive rod-cone degeneration (PRCD), the form of progressive retinal atrophy (PRA) present in the Poodle breed. The ERG findings are consistent with normal vision and not consistent with the severe visual deficits demonstrated by this dog.

CASE 2

A male Standard Poodle was referred to VHUP at 5 months of age with a history of blindness, abnormal gait, and a single seizure. Two additional seizures occurred after the initial presentation. Neurologic examination revealed blindness, normal PLR, absent menace responses, a hypermetric gait, and slow tactile placing responses in the forelimbs with all other reflexes normal. Ophthalmologic examination revealed no abnormalities. Cerebrospinal fluid (CSF) examination was within normal limits, and computerized tomography (CT) of the head showed asymmetric dilation of the lateral ventricles.

CASES 3 AND 4

A male and female Standard Poodle were littermates referred to VHUP at 3.5 months of age with a history of blindness and gait abnormalities. They had four

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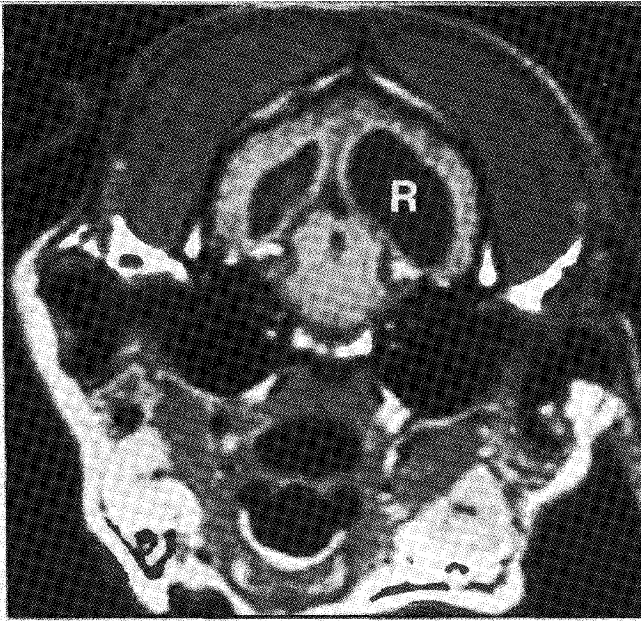


FIG. 1 — Magnetic resonance image (Case 4). The lateral ventricles are asymmetricaly dilated, with the right (R) more severe than the left.

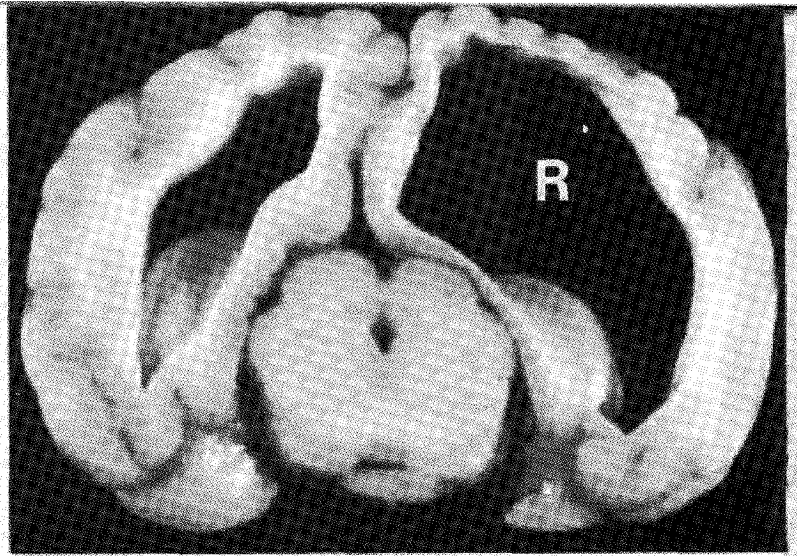


FIG. 4 — Brain, coronal section through the mesencephalon and caudal cerebral cortex (Case 4). There is asymmetrical dilation of the lateral ventricles, with the right (R) more severe than the left. The dorsal and lateral cerebral cortex contains multiple small gyri and shallow sulci.

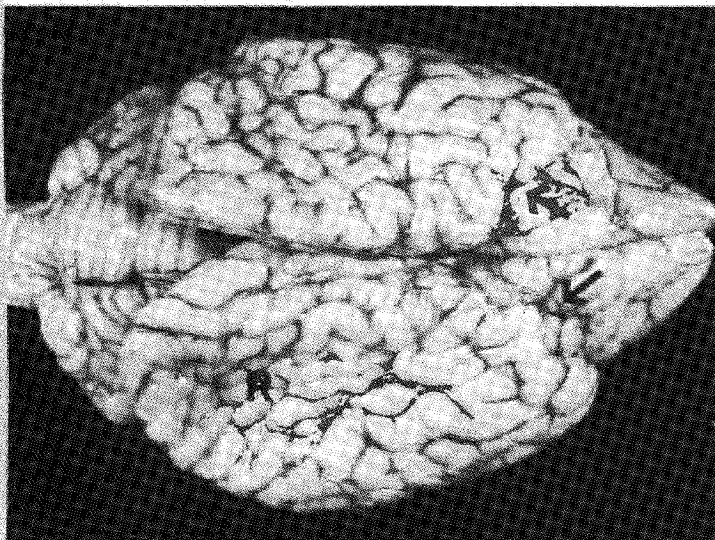


FIG. 2 — Brain, dorsal view (Case 3). The entire dorsal cerebral cortex caudal to the cruciate sulcus (arrows) is occupied by multiple small irregular gyri (polymicrogyri). The right caudal cortical surface (R) is depressed due to decompression of the severely dilated right lateral ventricle.

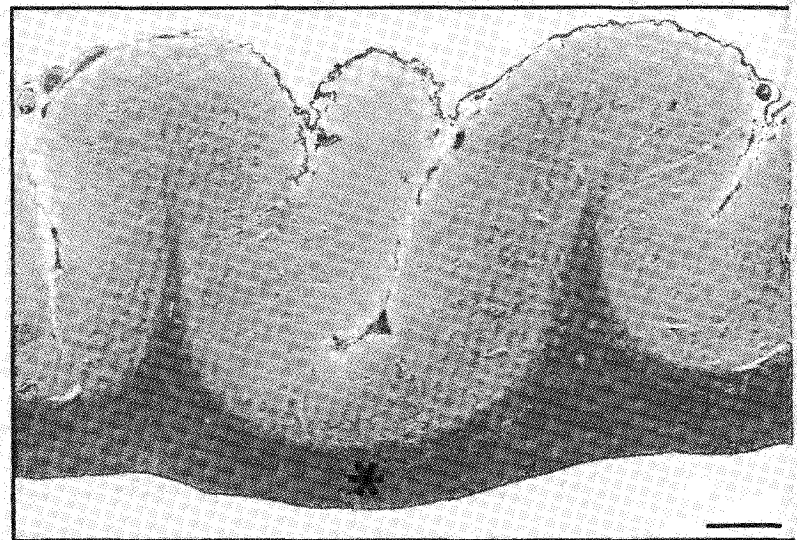
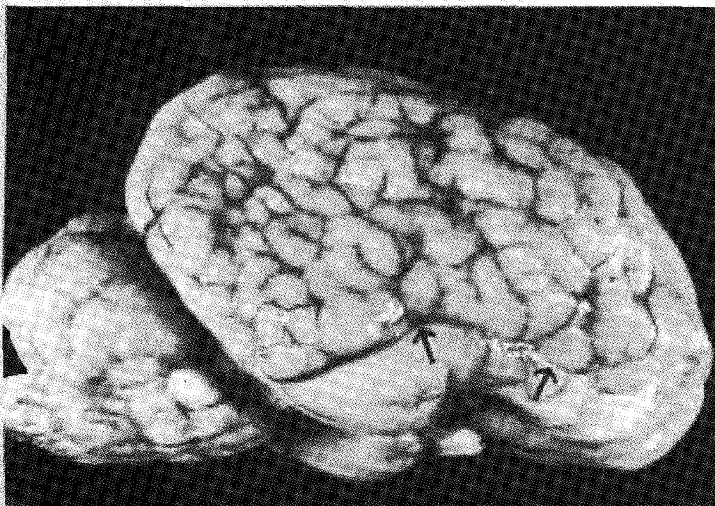


FIG. 5 — Photomicrograph of the occipital cortex (Case 3). Multiple small gyri with shallow irregular sulci overlie thin but normally myelinated cerebral white matter (*). (Luxol blue PAS hematoxylin; bar = 500 μ m)

FIG. 3 — Brain, lateral view (Case 2). Polymicrogyri cover the cerebral cortex dorsal to the rhinal sulcus (arrows).



male and four female littermates which were clinically normal. Neurologic examination demonstrated normal PLR, absent menace responses, and blindness in both animals. Both dogs walked with forelimb hypermetria and had no tactile placing responses in the forelimbs but were otherwise normal. Ophthalmologic examinations and ERG testing were normal in both dogs. Urine metabolic screening tests and quantitation of urinary amino and organic acids were unremarkable in both. Cerebrospinal fluid examinations were also within normal limits, but CT scans revealed asymmetrical ventricular dilation. This was confirmed in Case 4 by magnetic resonance imaging (MRI) (Fig. 1).

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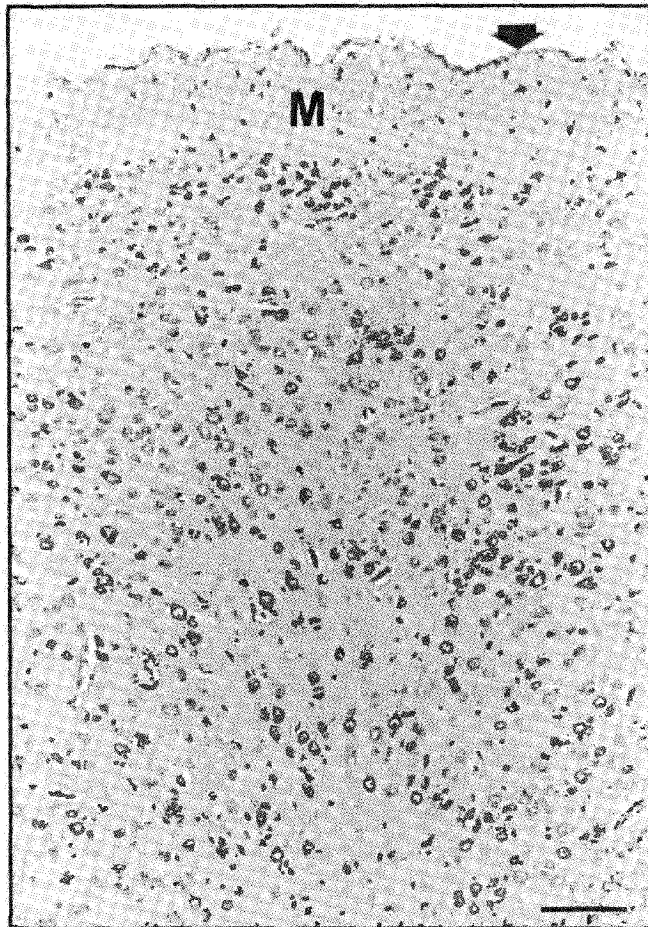


FIG. 6 — Photomicrograph of the occipital grey matter (Case 3). A normal molecular layer (M) is present under the pia mater (arrowhead). The underlying neurons are closely packed and not organized into discernible layers. (Cresyl violet; bar = 100 μ m)

Additional clinical tests performed on all dogs included CBCs and clinical chemistries. The CBCs were all within normal limits except for transient alterations associated with acute parvoviral infection in Case 1. Results of serum biochemical tests were all within normal limits for young dogs except for mild elevation of cholesterol (range 293-330) in all dogs. All dogs were humanely killed and necropsied.

Strikingly similar gross and histologic lesions were present in the brains of all four dogs. The normal gyral pattern of the dorsal and lateral cerebral cortex was replaced by multiple small irregular gyri (Fig. 2) which covered the entire dorsal caudal (occipital lobe) and middle (parietal lobe) surface extending rostrally to the cruciate sulcus in three dogs (Cases 2, 3, and 4). In one dog (Case 1), only the occipital cortex caudal to the rostral suprasylvian sulcus was affected. This pattern of small irregular gyri extended ventrally to the

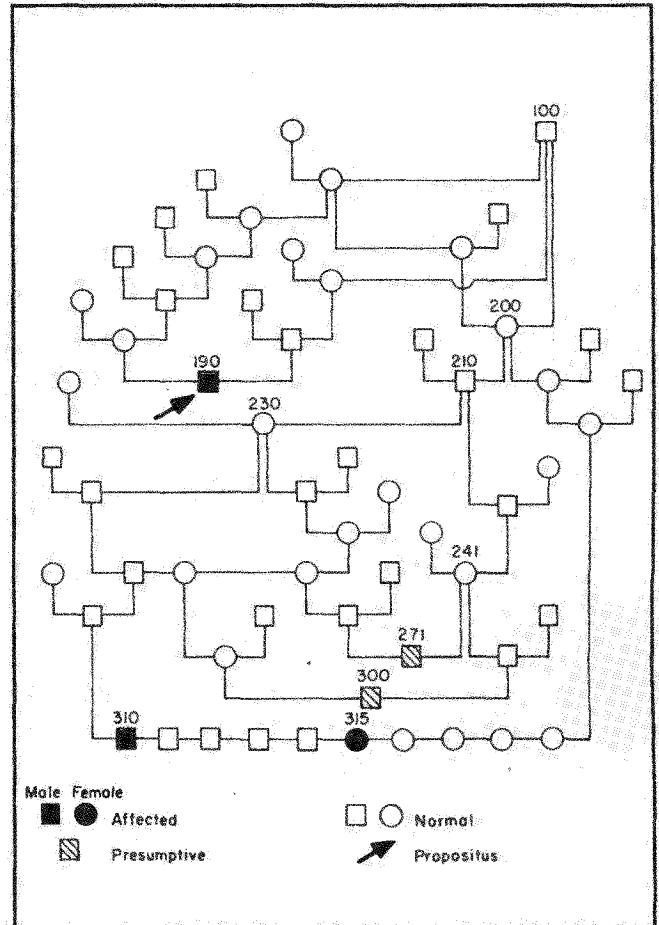


FIG. 7 — Pedigree of this family of Standard Poodles. Dog 100 is an ancestor common to the parents of the related dogs in this report (Cases 1, 3, and 4 are designated as Dogs 190, 310, and 315, respectively). Dogs 271 and 300 had identical clinical signs but received only a complete ophthalmic examination.

rhinal sulcus (Fig. 3). The bony ridges of the overlying skull conformed to the microgyral pattern of the underlying cortex. The caudal cerebral cortex was fluctuant in all dogs and, when sectioned, the lateral ventricles were found to be asymmetrically dilated; the caudal aspect of the right lateral ventricle was most severely affected in all four dogs (Fig. 4). The third ventricle, mesencephalic aqueduct, fourth ventricle, and lateral apertures were within normal limits in all four dogs. The cerebral cortex contained multiple irregular gyri and shallow sulci in affected areas, and the cortical grey matter and white matter including the corona radiata and caudal corpus callosum were thinner than normal in these areas.

Histologically, the affected cerebral cortex was similar in all dogs. The cortical grey matter was thinner than normal, and neurons appeared to be more densely packed than normal in some areas (Figs. 5 & 6).

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In all areas the molecular layer was visible beneath the pia mater, and in some areas it extended small projections into the underlying neuronal layers. The remaining five cortical layers were not discernible in all areas, although some evidence of lamination was seen in all animals. The white matter was thinner than normal with no evidence of demyelination. There was no evidence of astrocytosis or astrocytic scarring in the white or grey matter. The ependymal lining of the lateral ventricles was intact, except where artifactually separated, and consisted of low columnar to flattened cuboidal cells. No significant lesions were observed in the nervous system outside the cerebrum. The eyes, optic nerves, optic tracts, and lateral geniculate nuclei were normal. Early PRA lesions, as seen in Case 1, are not usually detectable in paraffin embedded hematoxylin and eosin sections.

No significant lesions were present in these dogs outside the central nervous system except for lesions typical of dogs recovering from parvoviral enteritis with secondary septicemia in Case 1 and a small (1 cm diameter) cardiac ventricular septal defect located just below the atrioventricular valves in Case 2.

Pedigree information was available for Cases 1, 3, and 4 (designated in Fig. 7 as dogs 190, 310, and 315, respectively). No pedigree information was available for Case 2. In addition, one author (Gustavo D. Aguirre) examined two related young male Standard Poodles (271 and 300 in Fig. 7) which were blind, had normal PLR, absent menace responses, and normal fundoscopic examination results. The parents of all these dogs were reported to have normal vision and gait. Dog 100 in Figure 7 is an ancestor common to both parents of each affected dog. In the litter for which we have complete information, two of 10 puppies (310 and 315 in Fig. 7), a male and a female, were affected. Together, these findings are consistent with the hypothesis that cortical blindness caused by abnormal development of the visual cortex is inherited as an autosomal recessive trait in this family of Standard Poodles.

Discussion

Polymicrogyria is rarely reported in domestic animals. To the best of our knowledge, this is the first report of this condition in the dog. Dilatation of the lateral ventricles, however, is common in dogs but is usually symmetrical and not associated with cortical dysplasia. The pathogenesis of the cortical abnormalities in these dogs is unknown, but pedigree analysis suggests that this is an inherited trait transmitted in an autosomal recessive manner. Polymicrogyria in cattle

is also thought to be inherited in an autosomal recessive pattern.²⁻⁴

Based on the normal PLR and normal ophthalmoscopic and ERG results, the blindness in these dogs was thought to be due to cortical disease. The decreased rod function detected in the ERG of Case 1 was incompatible with the severe visual deficits of this dog and represented early PRA, which is relatively common in Poodles, particularly the Miniature and Toy varieties. The lack of gross or histologic lesions in the eyes, optic nerves, optic tracts, lateral geniculate nuclei, and rostral colliculi, as well as the presence of severe polymicrogyria in the visual cortex of all four dogs, confirmed the clinical diagnosis of cortical blindness.

The cause of seizures in Case 2 and the cause of gait abnormalities in Cases 2, 3, and 4 are more difficult to explain. Cortical abnormalities are frequently cited as a cause of seizures, but only one of the four dogs demonstrated seizure activity. Idiopathic epilepsy is also common in the Standard Poodle,¹⁰ and concurrent idiopathic epilepsy cannot be excluded. Neurologic examinations of these dogs failed to demonstrate evidence for muscular, peripheral nerve, or spinal cord abnormalities, and no gross or histologic abnormalities were seen in these tissues when they were available for examination. Involvement of the motor cortex in the three dogs with gait and postural abnormalities (Cases 2, 3, and 4) suggests they may have been due to cortical disease. Although cerebral lesions commonly cause postural reaction abnormalities, they rarely cause a gait abnormality in domestic animals. Although the forelimb hypermetria may have been an adaptive response developed while learning to ambulate without visual cues, many blind animals walk normally. Hypermetria is a common sign of cerebellar lesions but the absence of other cerebellar signs and normal gross and microscopic examination of this structure make this an unlikely cause.

Primary gyri and sulci are present at birth in the dog and develop extensively in the first 3 to 6 weeks.¹⁰ The presence of clinical signs in these dogs in the first few months of life suggests that damage to the cortex occurred either in utero or in the first few weeks of life. The lack of astrocytic scarring or demyelination also suggests that the microgyria formed early in cortical development.

The distinction between polymicrogyria/microgyria and polygyria in humans is based on histologic criteria. Polygyria is thought to be secondary to hydrocephalus and has normal cortical lamination, while polymicrogyria/microgyria has abnormal lamination of the cortex. Polymicrogyria is usually described according to the pattern of the remaining neuronal layers in the affected cortex. The normal human cerebral cor-

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tex has six layers; four, two, and unlayered microgyric cortices have been reported, with considerable disagreement over which is the most common pattern.^{1,8} Many human cases have a two-layered cortex consisting of a superficial molecular layer with a thin unlaminated neuronal layer beneath.¹ Although up to six layers can be recognized in the canine cerebral neocortex, there are considerable variations in different regions.¹⁰ In the normal visual cortex of dogs, the neurons below the molecular layer may be arranged in up to five discernible layers, but in many areas they are arranged in columns with little evidence of lamination.

The cytoarchitecture of the cerebral cortex in these dogs differs somewhat from the usual descriptions of polymicrogyria in humans. In some areas a two-layered cortex, consisting of an outer molecular area and an inner unlaminated neuronal layer, was present; this arrangement is similar to some human cases.¹ In other affected areas, some evidence of neuron lamination was present, but no consistent abnormal layering pattern was present in all areas or in all dogs. There is also considerable variation in the number of neuronal layers present in the occipital cortex of normal dogs. The details of the architectural abnormalities which lead to blindness in these dogs is not known. Possibilities include abnormal afferent connections between the lateral geniculate nuclei and the visual cortex (often described as columns), absence of the appropriate cells or cellular connections within the visual cortex, and absence or inappropriate efferent connections of the visual cortex to other parts of the brain.

Two theories are commonly mentioned in discussions of microgyria in humans: abnormal migration of postmitotic cortical neurons, and destruction of neurons after migration but before the cortex is completely formed.^{1,8,11} Based on observations of spontaneous microgyria in humans⁹ and induced microgyria in rats,^{6,7} it has been suggested that four-layered microgyria occur when the cortex is injured near the end of neuronal migration and that unlayered microgyria occurs when the insult occurs prior to neuronal migration. Polymicrogyria frequently occurs with a pattern consistent with the distribution of the cerebral arteries. This has led to the suggestion that occlusion or partial occlusion of one or more cerebral arteries leads to ischemic destruction of the cortex either by damaging the radial glia which guide neuronal migration, thereby interrupting neuronal migration, or by causing necrosis of either migrating or postmigrational neurons.^{1,11} The former theory is supported by two studies in the rat. Experimentally induced necrosis of the superficial cerebral cortex immediately prior to the arrival of the final waves of migrating neurons caused a four-layered

microgyric cortex.^{6,7} When the superficial cortex was damaged after migration was complete, microgyria did not occur and the defect healed with glial cells.⁷ The pattern of polymicrogyria in these dogs was not consistent with the adult distribution of the caudal, middle, or anterior cerebral arteries.

In addition to the four Standard Poodles we examined in detail, we are aware of another dog with similar clinical signs and cerebral lesions. An 8-month-old male Golden Retriever was referred to VHUP for multiple gait abnormalities. Six of 11 littermates were reported to have similar clinical signs. This animal had abnormal menace responses with normal PLR, dilated lateral ventricles, and polymicrogyria involving the parietal and occipital cortex. The histologic findings were similar to those of the four Standard Poodles described previously.

Conclusion

The clinical and pathologic findings in four young Standard Poodles with cerebral polymicrogyria and asymmetrical ventricular dilation causing cortical blindness have been presented. Analysis of the pedigrees revealed that three of these dogs and two other Standard Poodles which were examined clinically were related and that polymicrogyria is probably inherited as an autosomal recessive trait in this family. ■

ACKNOWLEDGMENT

We dedicate this manuscript to the memory of the late Dr. John T. McGrath, who was instrumental in the evaluations of Cases 1 and 2 in this report and was an inspiration for many of us in the field of comparative neurology and neuropathology. We thank Drs. Brian Summers and Alexander de Lahunta for reviewing slides from these cases and for their helpful comments. We thank Dr. George Farnbach for the clinical evaluation of Case 2 and Juli Burns and James Hayden for their excellent technical assistance. These studies were partially supported by the NIH Referral Center-Animal Models of Human Genetic Disease (RR02512) and Grants EY-01244 and EY-06855.

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