

Ocular melanosis in the Cairn Terrier: clinical description and investigation of mode of inheritance

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Abstract

Objective To describe the clinical features of ocular melanosis in Cairn Terriers.

Animal studied One hundred and fourteen Cairn Terriers diagnosed with ocular melanosis.

Procedure(s) A complete eye examination was performed on each dog. Four dogs (and two unaffected control dogs) underwent a high frequency ultrasound examination of the anterior segment. The pedigrees of affected dogs were analyzed.

Results Forty-four (38.6%) dogs were male and 67 (58.7%) female; the sex of three dogs (2.6%) was not provided. A four-stage grading system of the ocular changes was developed. There was a variable age of onset, and the earliest change was a dark-colored thickening of the iris root. This was followed by the development of episcleral/scleral pigment plaques, release of pigment into the aqueous and deposition in the drainage apparatus, particularly ventrally. Secondary glaucoma developed in the most severely affected dogs. A slow progression of pigmentation in the tapetal fundus was observed and in some dogs pigment on the surface of the optic nerve head was seen. Three dogs developed uveal melanocytic neoplasms. Pedigree analysis suggested a possible autosomal dominant mode of inheritance.

Conclusions Ocular melanosis is an inherited, probably autosomal-dominant condition with a variable age of onset and rate of progression. It results in a thickening and pigmentation of the iris, release of pigmented material into the aqueous, pigment deposition in the sclera/episclera, and to a lesser extent posterior segment pigment deposition. Following extensive pigment deposition in the aqueous drainage pathways it can result in secondary glaucoma.

Key Words: Cairn Terrier, dog, ocular melanosis, pigmentary glaucoma, secondary glaucoma

INTRODUCTION

Covitz *et al.* in 1984 described at a meeting of the American College of Veterinary Ophthalmologists a condition in Cairn Terriers characterized by ocular pigment proliferation and secondary glaucoma which they termed pigmentary glaucoma.¹ Since that initial description of seven cases a few additional case reports have appeared in the literature describing the condition in an additional 10 Cairn Terriers, and the term ocular melanosis has come into common usage.^{2–4} From these case reports it is known that the condition is manifest as a progressive, bilateral proliferation of pigmented cells, primarily within the anterior uveal tract, and can result in the development of secondary glaucoma.

The incidence of ocular melanosis within the Cairn Terrier breed is not known, although there appears to be increasing

concern about it amongst Cairn Terrier breeders. A survey of members in 2005 by the Health Related Committee of the Cairn Terrier Club of America revealed that ocular melanosis was the second most common health issue of concern to the respondents. In an analysis of the incidences of glaucoma in pure-bred dogs reported to the Veterinary Medical Database, Gelatt and MacKay⁵ found that the reported incidence of glaucoma in Cairn Terriers examined at the participating North American Veterinary College Veterinary Teaching Hospitals had risen from 0.51% (mean for all breeds 0.46%) between 1974 and 1983 to 1.82% (mean for all breeds 0.89%) between 1994 and 2003. This increased incidence of glaucoma elevated the Cairn Terrier from 23rd in the league table of glaucoma incidence in pure-bred dogs to 9th. The survey did not report the cause of glaucoma so it is not possible to know what proportion of

these cases had developed glaucoma secondarily to ocular melanosis. Ocular melanosis is clearly breed related and a familial incidence is reported;² however, the mode of inheritance of the condition has not been demonstrated.

The purpose of the current study was to describe the ocular melanosis phenotype and investigate the mode of inheritance. Using the clinical findings from 114 Cairn Terriers diagnosed with ocular melanosis we have divided the condition into four stages and analyzed the mode of inheritance.

MATERIALS AND METHODS

Animals

Cairn Terriers included in this study comprised those referred to the Comparative Ophthalmology Service at Michigan State University, those examined (by SPJ) at screening sessions organized by the Cairn Terrier Club of America, and those examined by other veterinary ophthalmologists at their clinics or at screening sessions, who then submitted details of the ophthalmic findings for this study.

In addition to routine eye examination techniques, including gonioscopy, in the dogs examined at Michigan State University, high frequency ultrasound was performed on five affected dogs and, for comparative purposes, on two unaffected dogs (using a 35-MHz water path probe, E-Technologies Inc., Bettendorf, IA, USA). Information of repeat eye examinations on 23 dogs was available and analyzed to monitor progression of the condition.

Pedigree analysis

Pedigrees, where available, were obtained from affected dogs, and pedigrees linking affected animals were drawn using Progeny 6.0 software (Progeny Software, LLC, South Bend, IN, USA) and analyzed to establish a mode of inheritance.

Data analysis

Investigation of the ratio of affected to unaffected offspring produced by matings between unaffected and affected dogs was analyzed to investigate mode of inheritance by a chi-square test.

RESULTS

The results of eye examinations from a total of 114 dogs with confirmed ocular melanosis were included. Dogs were included where a clinical description of the ocular changes was available. Of the 114 ocular melanosis-affected Cairn Terriers included, 44 (38.6%) were male and 67 (58.7%) were female; the sex of three dogs (2.6%) was not provided. For 23 dogs information on three or more examinations was available.

The disorder represents a continuum of progressive changes but in order to investigate the progression of the condition a grading scheme of the clinical changes was drawn up as follows:

Stage 1: The presence of a characteristic dark-colored donut-shaped thickening of the iris root. Scleral/episcleral pigment deposits were not apparent. At this stage intraocular pressures were normal and gonioscopy unremarkable.

Stage 2: Thickening of the iris root was present (as in stage 1) but small pigment plaques were present in the sclera/episclera, particularly ventrally (Fig. 1). The pigment plaques were initially spicule-shaped but tended to progress into roughly circular spots. In some dogs gonioscopy revealed pigment deposits coating the ventral pectinate fibers.

Stage 3: Dogs were classified as having stage 3 disease when the scleral/episcleral patches had become more extensive, typically being several millimeters in size (Fig. 2). In some dogs at this stage the iris had a 'lumpy bumpy' appearance while in others there was still a visible donut-shaped thickening of the iris root. The iris at the pupillary zone appeared thinned, although not to such an extent that it could be transilluminated, and some dogs had a reduced extent of pupillary constriction, or even dyscoria. Variably sized pigmented particles were often seen suspended in the aqueous humor. Gonioscopy revealed a deposition of pigmented particles that coated the ventral drainage angle and, as more material was deposited, pigment could be seen on the ventral corneal endothelial surface past the ventral scleral overhang (Figs. 2,3). Some dogs with this stage of ocular melanosis presented with episodes of anterior uveitis, showing signs of discomfort, episcleral congestion, in some cases mild corneal edema accompanied by flare, and the presence of large amounts of pigmented material in the aqueous. The pigment appeared to, at least in part, originate from the face of the iris and left regions of the iris face relatively depigmented. During this stage episodes of raised intraocular pressure were often noted.

Stage 4: The progression to stage four was characterized by the development of glaucoma. There was usually further increase in pigment deposition in the drainage angle and the development of larger scleral patches (Fig. 3). Changes typical of chronic glaucoma developed, including globe enlargement, lens subluxation, cupping of the optic disc, vision loss, scleral staphyloma formation and even phthisis bulbi.

The condition was invariably bilateral and similar between the two eyes in the degree of pigmentation. The progression to intractable glaucoma when it occurred was not always bilateral and did not usually occur at the same time.

In dogs where serial fundus photographs were taken it was apparent that the posterior segment was also affected with progressive pigment deposition that gradually encroached on the tapetum (Fig. 4). In some dogs pigment could also be seen on the optic nerve head.

High frequency ultrasound

The anterior segment of five Cairn Terriers with either stage 2 or stage 3 ocular melanosis was examined by high frequency ultrasound. In each case this clearly demonstrated the thickening of the iris root that could be observed on clinical

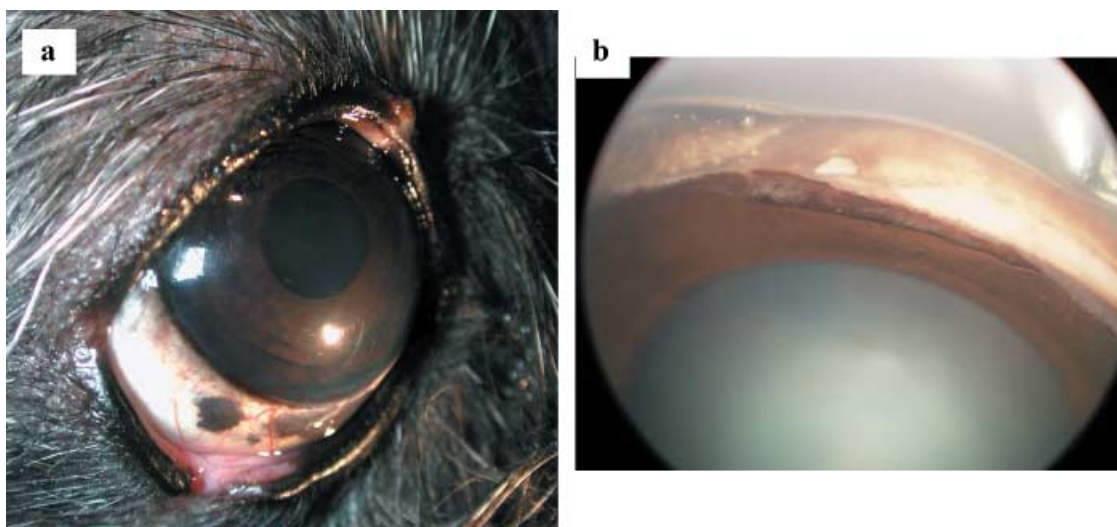


Figure 1. Stage 2 ocular melanosis. (a) External view of an eye with stage 2 ocular melanosis showing the characteristic circumferential thickening of the iris root and episcleral black-colored plaques. (b) View across the anterior chamber of the eye shown in (a) showing the circumferential thickening of the iris root. Examination of the opening into the ciliary cleft is obscured by the thickened iris root.

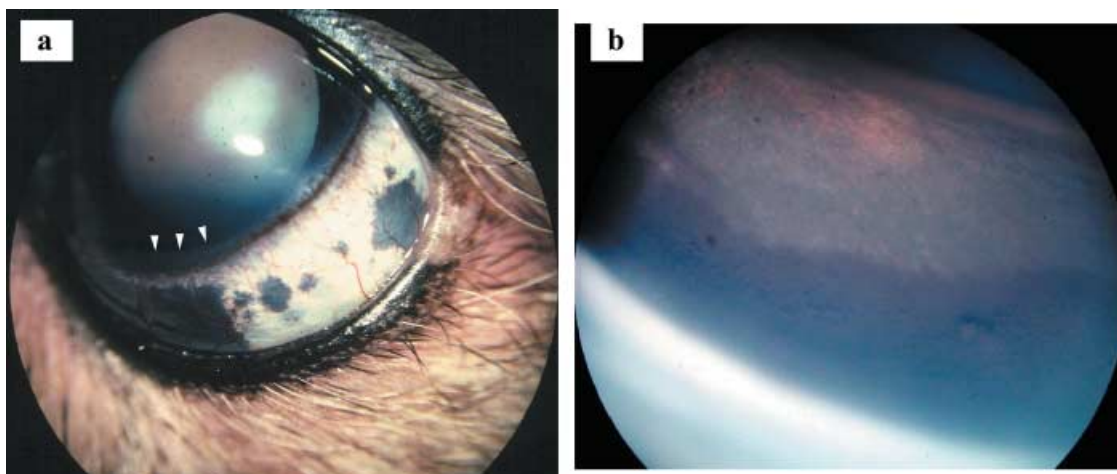


Figure 2. Stage 3 ocular melanosis. (a) An eye with stage 3 ocular melanosis. Large scleral/episcleral plaques are present ventrally. Pigment lines the ventral corneal endothelium to show beyond the limbus (indicated by white arrowheads). Large pigmented particles were suspended in the aqueous and can be seen in the photograph; these are highlighted in the pupil. (b) Gonioscopy view of the ventral drainage angle of the eye shown in (a). Deposited pigmented particles completely obscure the opening into the ciliary cleft.



examination and suggested that this was a solid thickening of the iris rather than a cystic swelling (Fig. 5).

Other changes

In affected dogs there were commonly pigmented skin plaques, although these were also seen in unaffected dogs. It was common to see darkly pigmented regions on the gums, although again this was a feature that could be seen in unaffected dogs. There was no obvious correlation of ocular

Figure 3. Stage 4 ocular melanosis. A very extensive ventral pigmented scleral/episcleral plaque is present. Pigment lining the ventral endothelial surface of the cornea is visible (white arrowheads). Secondary superficial vascularization and pigmentation is present.

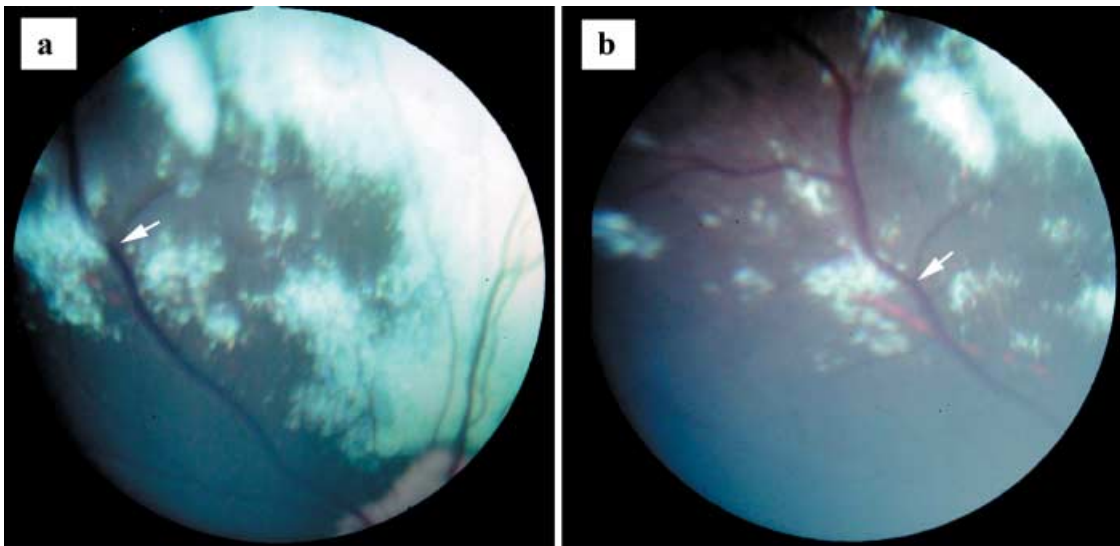


Figure 4. Progression of fundus pigmentation. Fundus photographs taken 19 months apart show progression of pigmentation that is obscuring or replacing the tapetum. The white arrows indicate the same position on the fundus photographs and are to help orientation.

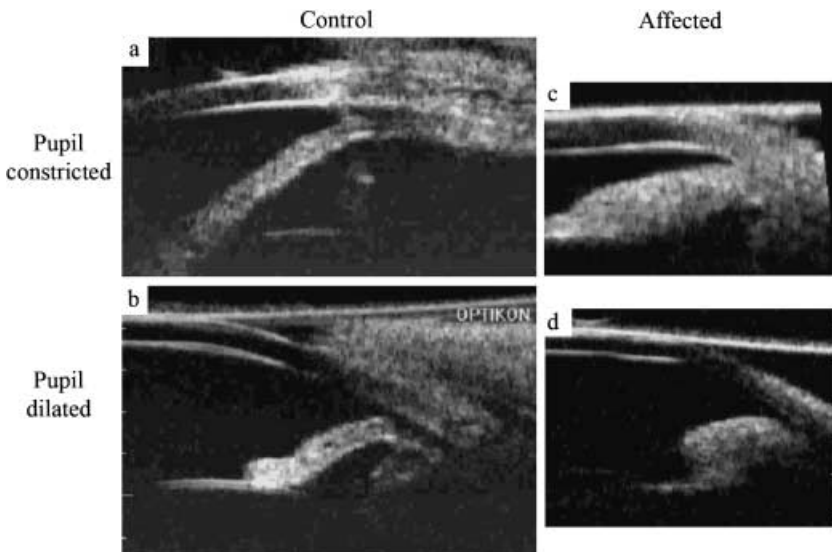


Figure 5. High frequency ultrasound images. (a) and (b) are images from a normal control; (c) and (d) from a dog with stage 2 ocular melanosis. Images (a) and (c) are taken with the pupil constricted (in response to a transilluminator), and (b) and (d) with the pupil dilated (imaged in the dark). Note the thickening of the iris root in the affected compared to the control animal.

melanosis with a particular coat color, and dogs with both light and dark coat coloration were affected. Investigation of correlation with coat color was complicated by the fact that the coat color of Cairn Terriers changes throughout life and this was a feature of the coat of both affected and unaffected dogs. Three ocular melanosis-affected dogs developed intraocular tumors; in each instance they had more advanced stages of ocular melanosis (stages 3 or 4). These were diagnosed as uveal melanomas or melanocytomas. In one dog widespread metastasis had developed.

Age at onset and rate of progression

There was a notable variation in either the rate of progression or age of onset. To investigate this further the stage of disease at first diagnosis was plotted against the age at which the condition was first diagnosed (Fig. 6). The condition was

first diagnosed in dogs between 1 and 16 years of age. Stage one disease was detected in dogs from as early as 1 year to as late as 10 years of age, suggesting that there is a range in age of onset. The progression to stage 4 ocular melanosis occurred in some cases at as early as 7 years of age while some dogs in their mid teens only had early stage (stage 2) disease, with one dog being first diagnosed with stage 2 disease at 16 years of age. The stage of disease of the dogs examined on more than three occasions was plotted against age at examination (Fig. 7). This failed to show an obvious correlation between rate of progression with age of onset.

Pedigree analysis

Pedigrees from dogs submitted were examined and drawn up into family groups linking affected dogs. Where possible dogs related to those diagnosed with the condition were

Figure 6. Graph of age and stage of disease at first diagnosis of ocular melanosis. The graph plots the age at which each of 114 Cairn Terriers was first diagnosed with ocular melanosis and the stage of disease at that first diagnosis. The percentage of cases at each disease stage for each age range is plotted. The number of dogs first diagnosed with ocular melanosis in each age range is shown in parentheses.

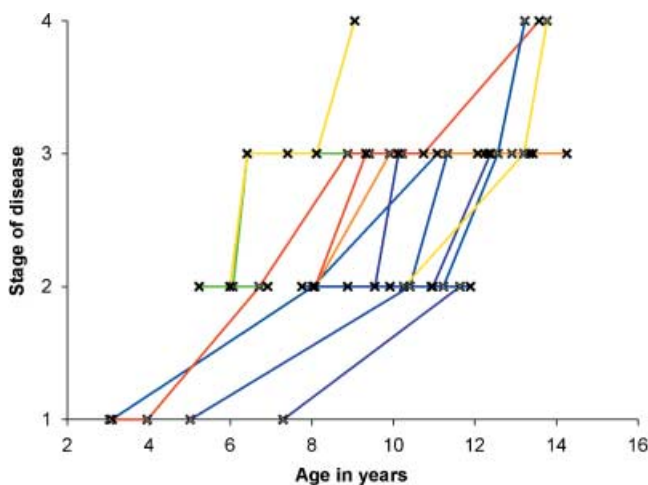
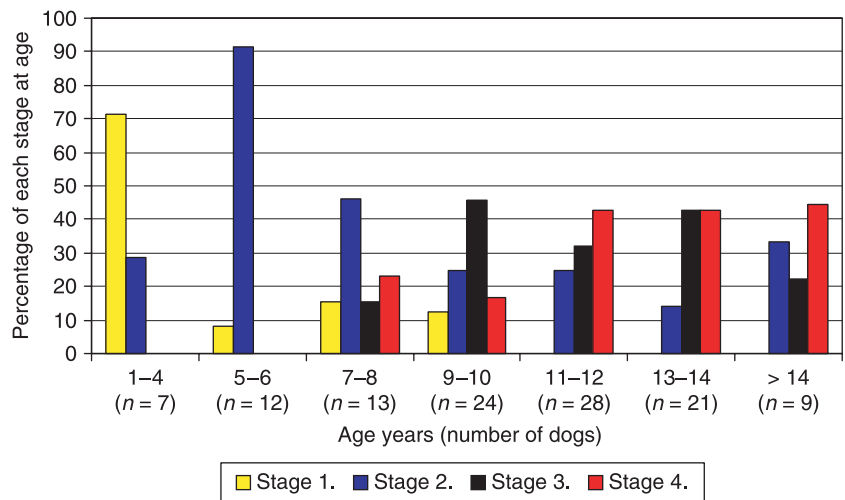


Figure 7. Graph showing the progression of the condition in dogs examined on three or more occasions. Each different colored line represents a single animal. The x marks along the lines indicate the timing of examinations.

examined and added to the pedigree. A family group pedigree is shown in Fig. 8. The sex incidence of the condition, as already described above, supports an autosomal mode of inheritance (rather than sex-linked). Examination of the families in which the condition was segregating

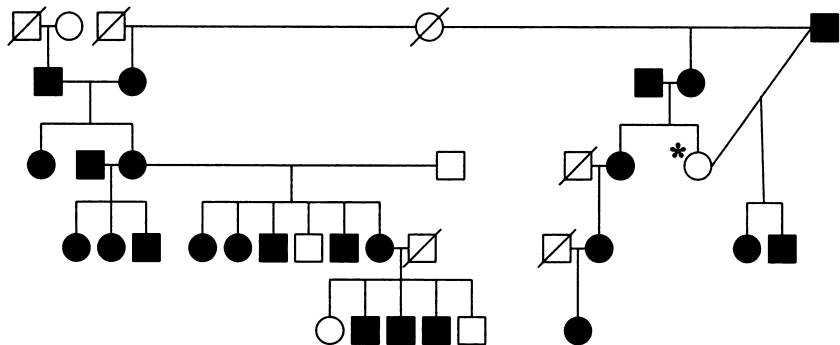
showed features suggestive of dominant inheritance; there were no incidences of the condition skipping a generation (information on up to four generations were available; Fig. 8). There were no instances of unaffected parents producing affected offspring, but there was one instance of two affected parents producing an unaffected offspring (Fig. 8). An analysis of the disease status of the offspring of matings between two affected animals and of matings between one affected and one unaffected animal was performed. Matings were only included where all the littermates had been examined and the offspring were at least 8 years of age at last examination. Four litters produced by the mating of two affected dogs met these criteria and resulted in eight affected offspring and one unaffected offspring. There were five litters produced from crosses between affected and unaffected animals that produced 12 affected and six unaffected offspring; a ratio of affected to unaffected that is more suggestive of a dominant rather than a recessive trait.

The variable age at onset complicated the pedigree analysis.

DISCUSSION

Ocular melanosis in Cairn Terriers is characterized by a bilateral proliferation of pigment, particularly involving the

Figure 8. An example of a family in which ocular melanosis is segregating. Squares are male dogs and circles, female dogs. Filled symbols represent ocular melanosis-affected dogs. Open symbols are dogs over the age of 8 years that are unaffected. Symbols with an oblique line are dogs for which ocular melanosis status is unknown. Note that the condition does not 'skip' any generations; this pedigree shows up to four generations. Dog indicated with * is the unaffected daughter of a cross between two affected animals. These features support an autosomal dominant mode of inheritance.



anterior uvea. Affected dogs have a dark-colored iris. Diagnosis of very early-stage disease may be difficult as the mild circumferential (or donut shaped) thickening of the iris root might be considered a variation of normality. However, with time, the degree of pigmentation progresses and characteristic episcleral/scleral pigmented plaques develop. These plaques appear caudal to the limbus in the region overlying the ciliary cleft. It is conceivable that the pigment becomes visible in the superficial layers of the sclera by migrating along aqueous drainage pathways. Release of larger amounts of pigmented material into the aqueous is a feature of the more advanced condition and this becomes deposited ventrally in the anterior chamber. The ventral drainage angle becomes obscured with pigmented material and eventually in many, but not all dogs a sufficient proportion of the drainage apparatus becomes impeded with pigment to cause a secondary glaucoma. Pigment accumulation also occurs in the posterior segment of the eye and slowly obscures or replaces the tapetum to a variable extent. Pigment may also be seen overlying the optic nerve head in some dogs. Pigment at these sites may be due to separate regions of pigment proliferation in addition to the anterior uvea; however, in no instances was there any evidence of choroidal thickening (that could be detected on fundoscopic examination). Alternatively, it is conceivable that the pigment could reach those sites after being shed into the aqueous.

The development of anterior uveitis in dogs with stage 3 disease may have resulted from the large amount of pigment that is present in the anterior uvea of affected dogs. It is known that some of the intermediate products in the formation of melanin from tyrosine are potentially toxic⁶ and it is possible that this could explain the development of uveitis in some affected dogs. The affected dogs had signs of uveitis, discomfort, episcleral congestion and in some instances mild corneal edema, in addition to the presence of aqueous cell and flare. This distinguished them from other dogs with more advanced (stage 3) ocular melanosis where it was common to see pigmented material floating in the aqueous, but where there were no other signs of an active uveal inflammatory process (such as the dog in Fig. 2).

The fact that many ophthalmologists started treatment with topical antiglaucoma medications prior to the development of glaucoma (typically early stage 3 cases) may have delayed or prevented the progression into stage 4 disease in some cases. This makes it difficult to assess the true natural progression of the condition. To obviate this confounding factor the stage of disease at first diagnosis was examined. This clearly shows that there is a wide range of age of onset. Although it is tempting to theorize that dogs with an early onset of lesions would have a more rapidly progressing disease course than those that develop lesions later in life, we could not prove this by examination of the available data. Serial examination of affected dogs over longer periods of time would be needed to further test this theory. The variation in the age of onset of a trait is a common feature of many genetic diseases. The variability may be due to factors such

as background genetics or environmental influences. Another possibility, considering the likely mode of inheritance of ocular melanosis, is that dogs heterozygous for the causal mutation might develop the condition later in life than those homozygous for the mutation. Identification of the gene mutation will allow this possibility to be tested.

In three of the 114 affected dogs ocular melanomas also developed. In one case this was malignant and metastasized widely. Anterior uveal melanoma is the commonest anterior uveal tumor in dogs.⁷⁻⁹ It is possible that the increased pigmentation in the anterior uvea of dogs with ocular melanosis leads to an increased chance of the development of melanoma. Such transformation of regions of heavy pigmentation into melanoma is recognized in other sites and other species; for example, transformation of pigmented cells leading to the formation of iris melanoma in cats with iris melanosis is a concern.¹⁰⁻¹²

Analysis of the inheritance of ocular melanosis in affected Cairn Terrier families indicated that the condition is autosomal. Also, a dominant mode of inheritance is suspected on the basis that in the available pedigrees the condition was not seen to skip a generation. Mating of two unaffected animals did not produce any affected offspring in the pedigree; and an unaffected dog was produced by an affected to affected mating. However, statistical analysis of the ratios of affected to unaffected offspring from affected to unaffected matings was not significantly different from the ratio anticipated if the trait was recessive and all the unaffected parents were carriers of the trait. Although the unaffected dog produced from an affected to affected mating was 13 years of age at last examination (shortly before death), the possibility remains that the condition has a later onset than observed in this study or that it is incompletely penetrant. Considering all the pedigree information, a dominant mode of inheritance seems most likely.

A phenotype similar to ocular melanosis in Cairn Terriers has been described in the Boxer and Labrador Retriever.⁴ Anterior segment pigment dispersal and secondary glaucoma have also been described in both humans and mice. In humans the terms pigment dispersal syndrome and pigmentary glaucoma have been used.^{13,14} In humans it is suggested that pigment dispersal can arise from the exfoliation of the posterior epithelium of the iris due to mechanical contact with ciliary processes or lens zonules.¹⁵ This results in iris defects that can be transilluminated. Similar defects do not occur in Cairn Terriers with ocular melanosis, where there is in fact a thickening of the iris. Although the pupillary zone of the iris may show evidence of atrophy as the condition advances, it does not develop defects that can be transilluminated. High frequency ocular ultrasound in humans suggests defects such as reverse pupil block, and iridociliary contact may contribute to exfoliation from the iris.¹⁶ The characteristic thickening of the iris root seen in Cairn Terriers with ocular melanosis, both clinically and by high frequency ultrasound, is not mentioned in papers describing human patients with pigment dispersal or pigmentary glaucoma.¹⁵⁻¹⁷ Mice with similar

phenotypes have pigment dispersal resulting from mutations in genes involved in melanin production, namely glycoprotein (transmembrane) nmb (Gpnmb) and tyrosinase-related protein 1 (Tyrp1).^{18–20} Collagen XVIII/endostatin-deficient mice have a similar condition to pigment dispersion syndrome in humans. The lack of functional collagen XVIIIa results in separation of the iris pigment epithelium from the posterior surface of the iris, with attachment of the posterior iris basement membrane to the ciliary body and lens.²¹ High frequency ultrasound of Cairn Terriers with ocular melanosis did not reveal any evidence to suggest separation of the posterior iris epithelium from the iris. Phenotypically, the changes seen in Cairn Terriers with ocular melanosis most closely resemble that of Gpnmb or Tyrp1 mutant mice.

In summary, ocular melanosis is an inherited, possibly autosomal dominant condition with a variable age of onset. It results in iris pigment proliferation, release of pigmented material into the aqueous, and pigment deposition in the sclera/episclera, probably associated with aqueous drainage pathways and to a lesser extent posterior segment pigment deposition. Following extensive pigment deposition in the aqueous drainage pathways secondary glaucoma may develop.

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