Clinical manifestations of inherited glaucoma in the beagle

Kirk N. Gelatt, Robert L. Peiffer, Jr., Robert M. Gwin, Glenwood G. Gum, and Leslie W. Williams

Inherited glaucoma was exhibited in 55 beagles. The glaucomatous process was divided into early (6 to 12 months of age), moderate (13 to 30 months of age), and advanced (31 months of age). In early glaucoma the iridocorneal angles, as judged by gonioscopy, were open and without anomalies, intraocular pressure was elevated, and the tonographic facility of aqueous outflow was decreased. With moderate glaucoma, the iridocorneal angles were typically open; intraocular pressure was elevated; facility of aqueous outflow was decreased; and variable optic disc cupping and focal disinsertion of the zonules from the lens were seen. Advanced glaucoma exhibited narrow to closed iridocorneal angles, decreased facility of aqueous outflow, elevated intraocular pressure, lens dislocation, optic disc atrophy, and finally phthisis bulbi. The beagle in the early and moderate stages of glaucoma, before angle closure and lens dislocation, is an animal model for studies in open-angle glaucoma.

Key words: glaucoma, canine model, open angle, tonography, tonometry, gonioscopy.

The scientific community for several decades has utilized animal models to study glaucoma. In most investigations glaucoma had to be induced by injections of substances into the anterior chamber, alterations of the blood flow to the eye or about the limbus, trauma, and recently the injection of alpha-chymotrypsin into the eye. Hereditary buphthalmia in the rabbit to date has been the only source of a spontaneous glaucoma model. Unfortunately, inheritance of congenital glaucoma in the rabbit is also linked to a semilethal trait and about 30% systemic malformations. The glaucomas in the dog in the United States occur primarily in the American cocker spaniel, basset hound, wirehaired fox terrier, Sealyham terrier, and the beagle. The glaucomas in the dog are usually classified into (1) primary (no antecedent disease), (2) secondary (demonstrable cause), and (3) congenital (with iridocorneal anomalies). Glaucoma in the dog results from a large number of causes, similar to man. Glaucoma in the American cocker spaniel, on the basis of gonioscopy, is the narrow-angle type, with the iridocorneal angle eventu-
ally closing.\textsuperscript{15, 16, 23} Glaucoma in the basset hound is associated with goniodysgenesis and persistence of large mesodermal bands across the iridocorneal angle rather than the normal branching pectinate ligaments.\textsuperscript{19-21} Although these iridocorneal angle anomalies have been demonstrated in the basset hound by gonioscopy, histology, and scanning electron microscopy, their exact role in the alteration of aqueous humor outflow and onset of the glaucoma is not known. Basset hound glaucoma is frequently exhibited clinically with a concurrent iridocyclitis.\textsuperscript{14}

Glaucoma occurred in nine related beagles.\textsuperscript{24} Both eyes were similarly affected and in the advanced stages exhibited lens subluxations, posterior and anterior luxations. The iridocorneal angles were open; two dogs exhibited limited areas of persistent mesodermal bands in the angle. Since then, a colony of glaucomatous beagles has been developed.\textsuperscript{22} Affected beagles respond with elevated intraocular pressure to water loading.\textsuperscript{25} Following standardization of the tonography procedure, glaucomatous beagles exhibited significantly lower facilities of aqueous humor outflow.\textsuperscript{26}

The purpose of this report is to describe the clinical signs of glaucoma in the beagle at the early, moderate, and advanced stages of the disease.

Materials and methods

The colony over a period of 5 years consisted of 55 glaucomatous beagles, 15 carrier beagles (from affected x normal matings), and 12 laboratory quality control beagles. All dogs were examined at monthly to bimonthly intervals by slit-lamp biomicroscopy, gonioscopy, and direct and indirect ophthalmoscopy. Observations on each dog were recorded by external, iridocorneal angle (gonioscopic), and fundus photographs.

Intraocular pressure was estimated in all dogs by Mackay-Marg tonometry (Biotronics, Inc., Redding, Calif.) one to four times daily. Tonometry was performed with the dog in the sitting position and under topical 0.4 percent benoxinate anesthesia (Dorsey Laboratories, Lincoln, Neb.). Tonometric recordings were compared with a three-way analysis for variance and co-variance between the control and glaucomatous beagles as well as the carrier and glaucomatous groups. Significance of F values was assumed at the p <0.001 level.

Schiötz tonography (Berkeley Bio-Engineering, Inc., San Leandro, Calif.) was performed quarterly on affected, carrier, and control beagles with acepromazine (Ayerst Laboratories, New York, N. Y.), 0.5 mg./kg. intravenously, and 5 min. later.
Inherited glaucoma in the beagle

Table I. Gonioscopic findings in glaucomatous beagles

<table>
<thead>
<tr>
<th>Age (mo.)</th>
<th>Glaucoma group</th>
<th>Angle width</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6</td>
<td>Preglaucoma</td>
<td>Normal</td>
<td>No angle anomalies</td>
</tr>
<tr>
<td>7-12</td>
<td>Early glaucoma</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>13-18</td>
<td>Glaucoma</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>19-24</td>
<td>Glaucoma</td>
<td>Normal to narrow</td>
<td>Narrow areas are focal</td>
</tr>
<tr>
<td>25-30</td>
<td>Glaucoma to advanced glaucoma</td>
<td>Normal to narrow</td>
<td></td>
</tr>
<tr>
<td>31-36</td>
<td>Advanced glaucoma</td>
<td>Narrow</td>
<td></td>
</tr>
<tr>
<td>36+</td>
<td>Advanced glaucoma</td>
<td>Narrow to closed</td>
<td>Focal peripheral anterior synechiae</td>
</tr>
</tbody>
</table>

Ketamine (Parke, Davis & Co., Detroit, Mich.), 10 mg/kg, intramuscularly, with a procedure previously described. The coefficients of aqueous humor outflow of the three groups were compared statistically as previously described.

All dogs were divided into groups by ages at 6-month intervals. The affected beagles were classified into the following groups: (1) pre-glaucoma, consisting of beagles 0 to 6 months old from affected parents, (2) early glaucoma, consisting of beagles 6 to 12 months old, (3) moderate glaucoma with dogs from 13 to 30 months old, and (4) advanced glaucoma with beagles in excess of 31 months old.

Results

The applanation tonometric recordings (in millimeters of mercury) of the control, carrier, and glaucomatous beagles are depicted in Fig. 1. Intraocular pressure, as determined by tonometry, demonstrated significant increases in the later group when the affected dogs were about 5 months of age. The tonometric recordings of both normal and glaucomatous beagles from 2 to 4 months of age may not be highly reliable, since during this time the animals are being trained and handled for the first time. Of the different families in the glaucomatous strain, the offspring from one bitch exhibited earlier and more marked elevations in intraocular pressure.

After the lens became dislocated from the patella fossa, greater daily variability in intraocular pressure resulted. Intermittent marked elevations in intraocular pressure occurred, associated with lens and vitreous pupillary blockage and perhaps other factors such as iridocyclitis and vitreous humor in the anterior chamber. During these episodes, corneal edema, fixed pupil, episcleral congestion, and tenderness of the eye occurred with elevated intraocular pressures from 60 to 100 mm Hg. Treatment with topical miotics and diuretics was usually initiated to moderate these attacks.

The gonioscopic appearance of the iridocorneal angle was a dynamic process, with the open iridocorneal angle gradually narrowing and eventually closing (Table I). In preglaucomatous and early glaucomatous beagles the iridocorneal angle was open and without anomalies (Fig. 2). The inner and outer pigment zones and the trabecular areas were normal. Small, infrequent focal areas of consolidated pectinate ligaments spanned the iridocorneal angle; but they usually affected less than 5 to 10 percent of the angle circumference and occurred with equal frequency in the control laboratory quality beagle.

In the moderate stages of the disease, the iridocorneal angle width was more variable, but usually open. Various quadrants of the iridocorneal angle were open, narrow, or closed, but the entire circumference was not usually closed. In the advanced glaucomatous beagles the iridocorneal angle was usually narrow and infrequently closed. In some narrow iridocorneal angles the bases of the pectinate ligaments nearly touched the trabecular area, suggesting closure of the sclerociliary cleft (Fig. 3). Eventually the onset of phthisis bulbi and/or corneal edema prevented further evaluations of the iridocorneal angle.

Changes in the lens and its position in the patella fossa are summarized in Table II. In the preglaucomatous beagles no changes in the lens, zonules, or lens posi-
Table II. Changes in the lens during glaucoma in the beagle

<table>
<thead>
<tr>
<th>Changes in lens</th>
<th>Mean age (mo.)</th>
<th>Standard error</th>
</tr>
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<tbody>
<tr>
<td>Position:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;In situ&quot;</td>
<td>17.6</td>
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<tr>
<td>Focal zonulary disinsertion</td>
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<td>3.6</td>
</tr>
<tr>
<td>Posterior luxation</td>
<td>45.0</td>
<td>3.8</td>
</tr>
<tr>
<td>Aphakic crescents:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial</td>
<td>27.6</td>
<td>5.5</td>
</tr>
<tr>
<td>Lateral</td>
<td>27.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Cataract formation</td>
<td>27.6</td>
<td>3.8</td>
</tr>
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Changes in lens during glaucoma in the beagle.

Fig. 2. Iridocorneal angle of normal width, pigment zones, and pectinate ligaments in an 18-month-old affected beagle bitch.

Fig. 3. Iridocorneal angle of a 55-month-old advanced-glaucoma beagle bitch exhibiting heavy pigmentation and closure of the sclerociliary cleft.

Fig. 4. Iridocorneal angle of a normal beagle exhibiting the normal position of the lens in the patella fossa.

Fig. 5. Iridocorneal angle of a 55-month-old advanced-glaucoma beagle bitch exhibiting heavy pigmentation and closure of the sclerociliary cleft.

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As the glaucoma advanced, zonules continued to detach from the lens equator. When more than 180 degrees of the lens' zonular attachments were lost, subluxation of the lens from the patella fossa occurred and was exhibited as tilting, usually anteriorly, pushing focal areas of the iris forward. Iridodonesis was usually present.

In the advanced glaucomatous beagles, lens position was variable, with loss of most to all of its zonular attachments. Dislocation of the lens occurred into the anterior chamber most frequently (Fig. 6); occasionally the lens luxated posteriorly into the vitreous body (Fig. 7). Cataracts formed in most of the luxated lenses.

The ocular fundi, including the optic discs, were normal in the preglaucomatous and early glaucomatous beagles. Changes in the optic disc were variable but occurred earlier in glaucomatous beagles that developed early and extensive elevations in intraocular pressure. Some glaucomatous beagles demonstrated loss of the lateral optic disc rim. Others exhibited central to paracentral cupping of the optic disc (Fig. 8). Retinal blood vessels, especially the
Fig. 4. Focal disinsertions of two focal zonules in a 23-month-old glaucomatous beagle dog. Note absence of a stretched ciliary body process in the same area (arrows).

Fig. 5. Small aphakic crescent (arrows) in a 49-month-old glaucomatous beagle dog. Focal equatorial cataract formation is evident at the 7 o'clock position.

Fig. 6. Anterior lens luxation (arrows) and associated corneal edema in a 54-month-old glaucomatous beagle bitch.

Fig. 7. Posterior lens luxation and early cataract formation (arrows) in a 40-month-old advanced-glaucoma beagle bitch.

Fig. 8. Small retinal arterioles about the disc, gradually disappeared. The optic discs eventually became quite round, depressed, and not infrequently pigmented in advanced glaucomatous beagles. With optic atrophy, most retinal blood vessels disappeared; however, the primary veins and arterioles usually remained (Fig. 9). Blindness occurred with the optic atrophy.

Consecutive Schiøtz tonographic recordings of control, carrier, and glaucomatous beagles are summarized in Fig. 10. The carrier and control dogs exhibited similar coefficients of aqueous humor outflow that were significantly different from the glaucomatous beagles (p<0.001). The glaucomatous beagles yielded consistently low coefficients of aqueous humor outflow.
Fig. 8. Early cupping (arrows) of the optic disc in a 26-month-old glaucomatous beagle bitch. (Original fundus magnification ×38.)

Fig. 9. Optic atrophy in a 33-month-old glaucomatous beagle dog. Note the reduced retinal vasculature and the depressed optic disc. (Original fundus magnification ×18.)

which became lower as the glaucomatous beagles aged and the glaucoma worsened.

Discussion

Primary glaucoma in man exists as two distinct diseases: (1) primary chronic open-angle glaucoma and (2) primary narrow-angle glaucoma. Inherited glaucoma in the beagle is a primary type; although the mechanisms of decreased aqueous humor outflow have not been defined, precipitating factors are absent in the early stages of the disease. Dependent on the stage of the disease, the iridocorneal angle is open in the early and moderate glaucomatous stages but eventually narrows as the lens luxates in advanced glaucoma. As a result, the canine model has gonioscopic similarities to both open- and narrow-angle glaucoma in man, but most importantly to the primary open-angle type.

The accurate measurement of intraocular pressure in the glaucomatous dog is essential in the investigation of the disease. Use of the Schiøtz tonometer with tables derived from human eyes results in underestimation of actual intraocular pressure. Schiøtz tables specifically for the dog assist in minimizing this error; however, applanation tonometry offers additional advantages. The Mackay-Marg tonometer, of four applanation types evaluated for the normal eye, is superior in the dog. In the control, carrier, and glaucomatous beagles, intraocular pressures as measured by Mackay-Marg tonometry were significantly different after the glaucomatous dogs were 8 months old. The greater variance in the glaucomatous beagles may be related to poor intraocular pressure-regulating mechanisms, the lens luxation, occasional severe "acute" attacks, and vitreous humor in the anterior chamber.

The onset of elevated intraocular pressure and decreased facility of aqueous humor outflow precede the subluxation of the lens. Hence in the genesis of the disease, the lens luxation appears secondarily and simply aggravates the disease process. Consecutive ultrasonic studies currently in progress may provide additional information about the lens position and size, and axial length of the globe to the glaucoma.

Gonioscopy of affected beagles at different stages of the disease indicates an open iridocorneal angle that gradually narrows and eventually closes. Persistent mesodermal bands described in the basset hound glaucoma have not been detected in the beagle by gonioscopy, light micros-
Coefficient of Aqueous Outflow (μl/mm Hg/min.)

Fig. 10. Schi0tz tonographic recordings (μl/mm. Hg/min.) of carrier (A), control (B), and glaucomatous beagles (C) from ages of 4 to 36+ months old. Bars indicate standard error.

copy, or preliminary scanning electron microscopy. In pharmacologic studies with glaucomatous beagles, pilocarpine, epinephrine, dipivalyl epinephrine, and the carbonic anhydrase diuretics have been efficacious. Depend on the iridocorneal angle morphology and the stage of the glaucoma, certain cholinergic and adrenergic drugs might have certain advantages as well as contraindications.

The effects of elevated intraocular pressure on the dog optic disc have been controversial. In our experience detection of early and subtle changes in the variable shape optic disc of the dog necessitates serial fundus photographs. Eventually, however, extensive optic atrophy occurs and blindness follows. The finite details of optic disc cupping and destruction by the elevated intraocular pressure will require additional investigations using stereo photographs and fluorescein angiography. Nevertheless, progressive depression or cupping of the optic disc occurs in the glaucomatous beagle and eventually progresses to atrophy.

The glaucomatous beagle in the early stages of the disease, before angle closure and lens dislocation, may be a useful and important animal model for studies in open-angle glaucoma. Because the spontaneous disease is inherited without systemic abnormalities and is bilateral, experimental procedures to induce glaucoma are not necessary. This glaucoma model exhibits a reasonably predictable clinical course over a period of at least 2 to 3 years, thereby permitting numerous and serial investigations. Gonioscopic and preliminary scanning electron microscopic examinations support an open iridocorneal angle without congenital anomalies. Intraocular pressure of the glaucomatous beagles with open iridocorneal angles has been effectively lowered by several drugs, which include, in part, topical pilocarpine, epinephrine, dipivalyl epinephrine, and the carbonic anhydrase diuretics. The usefulness of the glaucomatous beagle as a pharmacologic model appears promising.

REFERENCES
7. Lessell, S., and Kuwabara, T.: Experimental...
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