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Vision outcome with antiglaucoma therapy and prognostic factors in canine glaucoma: A 6-years retrospective study in Japan

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Abstract

Vision outcome provides invaluable information in clinical decision making in the management of canine glaucoma. In the present study, data of glaucoma dogs were retrospectively evaluated for vision outcome by treatment modality (with or without surgical implantation of the Ahmed glaucoma valve, AGV) and by type of glaucoma, sex and breed in cases of medically treated glaucoma. Among 1990 dogs presented with eye diseases between 2011 and 2017, 224 dogs (11.3%) were diagnosed with glaucoma at initial presentation and 228 eyes of 207 dogs have follow-up records of at least 30 days were included in the analysis. At the time of first presentation, 62/228 eyes (27.2%) were visual. Visual preservation rates were constantly significantly higher in dogs that received AGV placement with a median time to vision loss of 76.4 weeks vs. 9.6 weeks in dogs that received medical treatment alone. Among dogs treated medically, vision outcome was comparable between two types of glaucoma (*i.e.*, primary and secondary) and between sexes. Medically treated Shiba dogs showed significantly lower vision preservation rates and a shorter median time to vision loss compared to other breeds. These results suggest that AGV implants result in better vision outcome compared to medical therapy alone and should be considered in dogs that are visual at the time of presentation and suitable for surgery. And Shiba dogs are considered as the factor that indicate poor vision outcome of medical treatment alone in the present study.

Key Words: Antiglaucoma therapy, canine glaucoma, prognostic factors, vision outcome

Introduction

The canine glaucomas are a group of ocular diseases characterized by increased levels of

intraocular pressure (IOP) resulting in disrupted axoplasmic flow in the optic nerve and degeneration or death of retinal ganglion cells and their axons that are detrimental to the

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maintenance of vision and health of the eye. Glaucomas can be classified into two types based on the possible etiology: primary, if the increase in IOP develops without concurrent diseases and is hereditary or breed-related; and secondary, if IOP elevation is associated with other ocular or systemic disease^{15,16}.

Glaucomas are incurable, and continued treatment is needed to maintain vision and control IOP. Especially in dogs, glaucomas may still progress to the end stage despite various antiglaucoma therapies and result in uncontrolled IOP and vision loss. Thus, the main and important goal of canine glaucoma therapy is to maintain suitable IOP and vision as long as possible. Current antiglaucoma treatment is primarily based on medical therapy using topical and oral antiglaucoma drugs. Recently, however, new surgical devices and systems have been developed and provided longer IOP control and vision maintenance than previous surgical techniques. Commonly employed techniques among veterinary ophthalmologists include anterior chamber shunts (e.g., Ahmed glaucoma valve, AGV, and ExPress device implantation) and endoscopic ciliary body photocoagulation. The success rate and outcome of each technique have been reported previously^{2,17,21}. However, these reports mainly focus on the results of each surgical technique or combined techniques and do not provide a full perspective that every practitioner needs when deciding the best treatment options. The purpose of the present study was to determine the prognostic factors of vision retention by retrospectively evaluating the outcomes of canine antiglaucoma therapies at a referral ophthalmology center. Factors evaluated included treatment modality (AGV implants or medical treatment alone) as well as type of glaucoma, sex and breed in cases that were treated only medically.

Materials and Methods

Subjects: Among 1990 dogs presented to a referral ophthalmology practice (Veterinary Eye Care Service) during the six years from October 2011 to October 2017, 224 dogs (11.3%) were diagnosed with glaucoma at initial presentation and 207 dogs (228 eyes) for which records of at least 30 days of follow-up evaluation were available were included in the study (Fig. 1). All dogs had received a routine eye examination including the menace response, dazzle reflex, IOP, slit lamp biomicroscopy and fundus examination.

Glaucoma classification and signalment: Subjects were classified based on the cause of glaucoma: 1) primary glaucoma; 2) secondary glaucoma and 3) glaucoma of unknown etiology, and the number of cases (eyes), age, sex and breed were analyzed. Breeds were reported only if there were at least 6 dogs, and breeds fewer than 6 dogs were reported as “others/other breeds.”

Vision at initial presentation: Vision at the first presentation was analyzed by type of glaucoma, sex and breed. Eyes were considered visual when the menace response and/or dazzle reflex were present, nonvisual when both were absent, and inconclusive (one of menace response or dazzle reflex was absent and another was inconclusive, or both were inconclusive). The dazzle reflex was examined by a handheld slit lamp (SL-15, Kowa Company, Aichi, Japan) with the maximum light output.

Comparison of vision outcome: Vision outcomes were compared between medical treatment alone and AGV implants in glaucoma dogs that were visual at the time of initial presentation. Dogs that received medical therapy alone were further divided by etiology (primary or secondary), sex and breed for a comparison of vision outcome. The medical therapy regimen included topical β -blockers (0.25% nipradilol, 0.5% timolol maleate

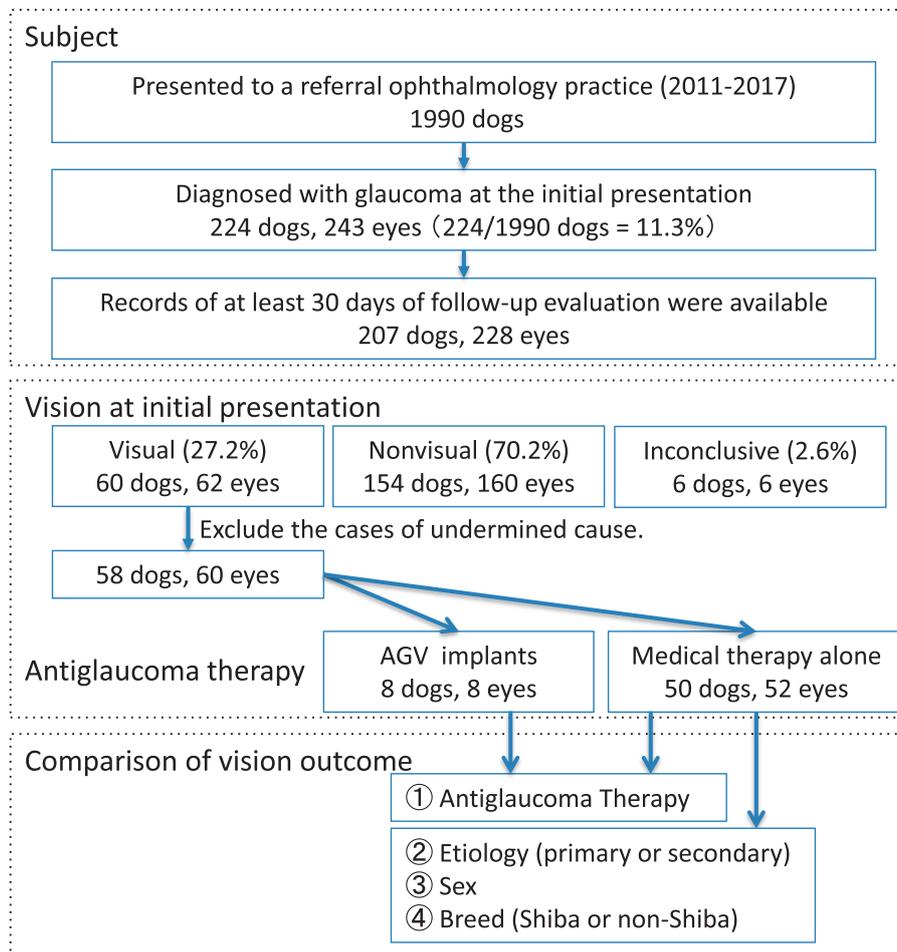


Fig. 1. Flowchart of the subjects, the classification for comparison of vision outcome. Among 1990 dogs presented during the six years, 224 dogs (11.3%) were diagnosed with glaucoma at initial presentation and 207 dogs (228 eyes) for which records of at least 30 days of follow-up evaluation were available were included in the study. Vision outcomes were compared between AGV implants and medical treatment alone in glaucoma dogs that were visual at the time of initial presentation (①). Dogs that received medical therapy alone were further divided by etiology (②), sex (③) and breed (④) for a comparison of vision outcome.

and 2% carteolol hydrochloride), carbonic anhydrase inhibitors (1–2% dorzolamide hydrochloride and 1% brinzolamide), prostaglandin analogues (0.005% latanoprost, 0.0015% tafluprost and 0.03% bimatoprost), large conductance calcium-activated potassium channel activators (0.12% isopropyl unoprostone), corticosteroids (0.05% difluprednate, 0.1% prednisolone acetate, 0.1% dexamethasone, 0.1% methylprednisolone), non-steroidal anti-inflammatory drugs (NSAIDs) (0.1% diclofenac and 0.1% pranoprofen) as well as oral prednisolone (1–2 mg/kg/day), intravenous methylprednisolone sodium succinate (10–15 mg/kg), oral or subcutaneous NSAIDs (carprofen,

firocoxib and robenacoxib) and systemic diuretics (50% oral glycerin and intravenous mannitol). All AGV procedures were performed by the same surgeon using a VFP8 valve (CARA Life, Rancho Cucamonga, CA, U.S.A.) and the standard technique⁴.

Statistical analysis: The analyses were conducted using BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). The mean age was compared by Student's *t*-test, while contingency tables were used to analyze sex and breed about glaucoma classification. A Chi-squared test was used for comparison among

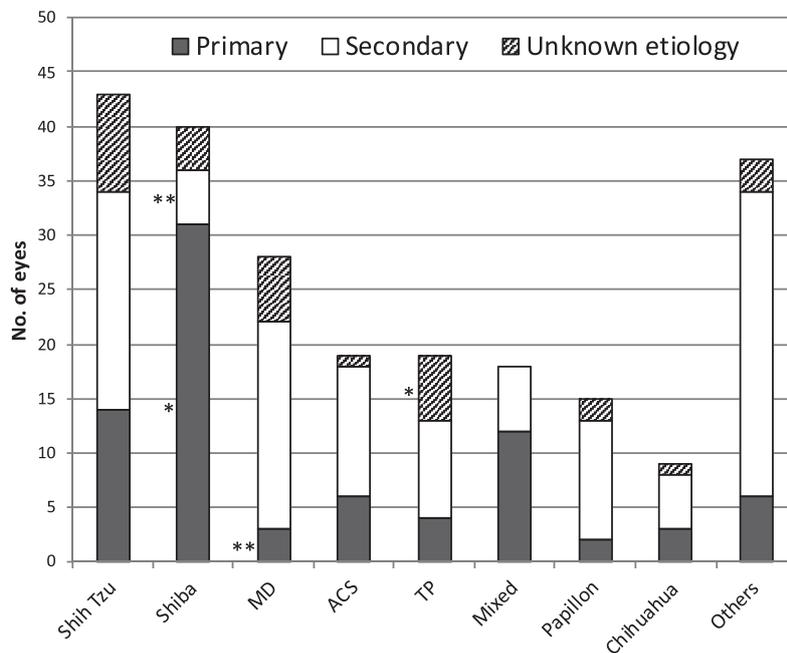


Fig. 2. Types of glaucoma and breed. The overall incidence was highest in Shih Tzu (18.9%) followed by Shiba (17.5%) and Miniature Dachshund (MD) (12.3%). Shiba had a higher incidence of primary glaucoma than secondary glaucoma. Among breeds shown, MD was least likely to develop primary glaucoma, while Toy Poodle (TP) was more likely to have glaucomas of unknown etiology. ACS: American Cocker Spaniel. Single asterisk (*) indicates significant overrepresentation, and double asterisks (**) indicate significant underrepresentation in comparison with other groups of breeds by contingency table analysis ($P < 0.05$).

type of glaucoma and sex, and contingency tables among breeds about vision at initial presentation. A Kaplan-Meier method and the log-rank test were used for comparison of vision outcome about treatment, etiology, sex and breed. P values less than 0.05 were considered significant in all statistical analysis.

Results

Etiology and signalment

Glaucomas were primary in 68 dogs (81 eyes, 35.5%) and secondary in 108 dogs (115 eyes, 50.4%). The cause was undetermined in the remaining 31 dogs (32 eyes, 14.0%). The mean age was 9.8 ± 0.3 , 10.4 ± 0.3 and 10.9 ± 0.4 years in dogs with primary glaucoma, secondary glaucoma and glaucoma of unknown etiology, respectively. No statistical significance was observed in age. In dogs with secondary glaucoma, concurrent medical conditions included cataract

(68 eyes, 59.1%), lens instability (44 eyes, 38.3%), retinal detachment (25 eyes, 21.7%), uveitis (7 eyes, 6.1%), surgically treated cataract (6 eyes, 5.2%), uveal tumor (6 eyes, 5.2%), pigmentary glaucoma (2 eyes, 1.7%) and corneal perforation (1 eye, 0.9%). The majority of glaucomas of unknown etiology was long-standing, and therefore the cause was difficult to determine due to lens instability and retinal detachment.

The number of glaucoma eyes and type of glaucoma in each breed group are shown in Fig. 2. The incidence was highest in Shih Tzu (18.9%) followed by Shiba (17.5%), Miniature Dachshund (12.3%), American Cocker Spaniel (8.3%), Toy Poodle (8.3%), Papillon (6.6%) and Chihuahua (3.9%). Mixed breeds accounted for 7.9%, and other breeds (16.2%) included Great Pyrenees, Flat-Coated Retriever, French Bulldog, Pomeranian, Pug, Maltese, Basenji, Miniature Schnauzer, Jack Russell Terrier, West Highland White Terrier, Welsh Corgi Pembroke, Cavalier King Charles Spaniel, Cairn Terrier, Golden

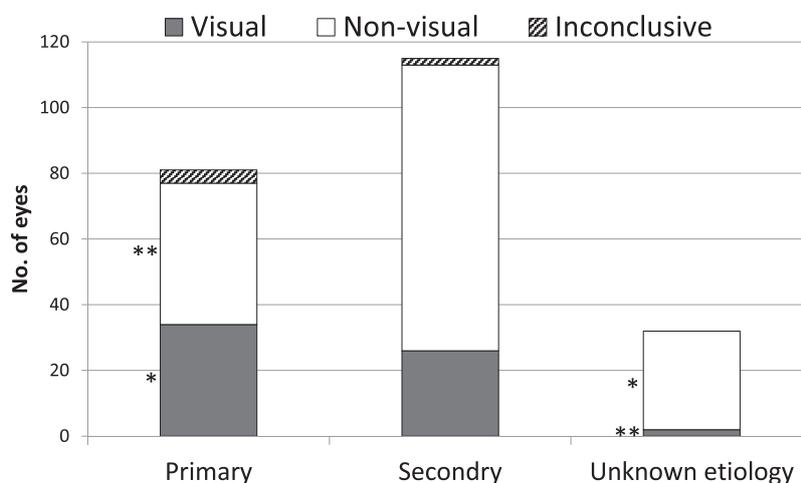


Fig. 3. Type of glaucoma and vision at the first presentation. Eyes with primary glaucoma were significantly more likely visual, while eyes with glaucoma of unknown etiology were less likely visual. Single asterisk (*) indicates significantly higher rates, and double asterisks (**) indicate significantly lower rates in comparison with other groups of etiology by contingency table analysis ($P < 0.05$).

Retriever, Labrador Retriever, Brussels Griffon, Border Collie, Boston Terrier, Miniature Pinscher, Yorkshire Terrier and Dalmatian. Shiba was significantly overrepresented in the primary glaucoma group and significantly underrepresented in the secondary glaucoma group. Miniature Dachshund was the breed significantly underrepresented in the primary glaucoma group, while Toy Poodle was significantly overrepresented in the group of glaucomas of unknown etiology.

One-hundred eyes were from males (74 eyes from neutered males), and 128 eyes from females (89 eyes from neutered females). There was no statistically significant sex predisposition among type of glaucoma.

Vision at the first presentation

Among 228 eyes of 207 dogs studied, 62 (27.2%) eyes of 60 dogs were visual at the initial presentation, whereas 160 eyes (70.2%) of 154 dogs were nonvisual. Vision was restored and maintained in 2 nonvisual eyes of 2 dogs after subsequent treatment. One of these cases was a Toy Poodle with primary glaucoma, and vision was maintained up to 42 days. The other was a Miniature Dachshund with glaucoma of unknown etiology, and vision was maintained up to 28 days.

Among the eyes that were visual at the first presentation, primary glaucoma was diagnosed in 34 eyes (42.0%), secondary glaucoma in 26 eyes (22.6%), and glaucoma of unknown etiology in 2 eyes (6.3%). Eyes with primary glaucoma were significantly more likely visual, while eyes with glaucoma of unknown etiology were less likely visual (Fig. 3).

By sex, 29 of the visual eyes were from males (19 eyes from neutered males), while 33 of the visual eyes were from females (25 eyes from neutered females). No significant sex predisposition was found.

Fig. 4 shows the vision status by breed at the first presentation. Shiba dogs were significantly more visual compared to other breed groups, indicating that vision was more likely maintained at the time of first presentation in this breed. In Shih Tzu, in contrast, vision was likely lost at the time of the first presentation with a lower number of visual eyes and a higher number of nonvisual eyes than in other breed groups. In mixed-breed dogs, vision status was more often inconclusive, and there was a lower number of nonvisual eyes compared to other breed groups.

Vision outcome

In 60 eyes of 58 dogs which excluded

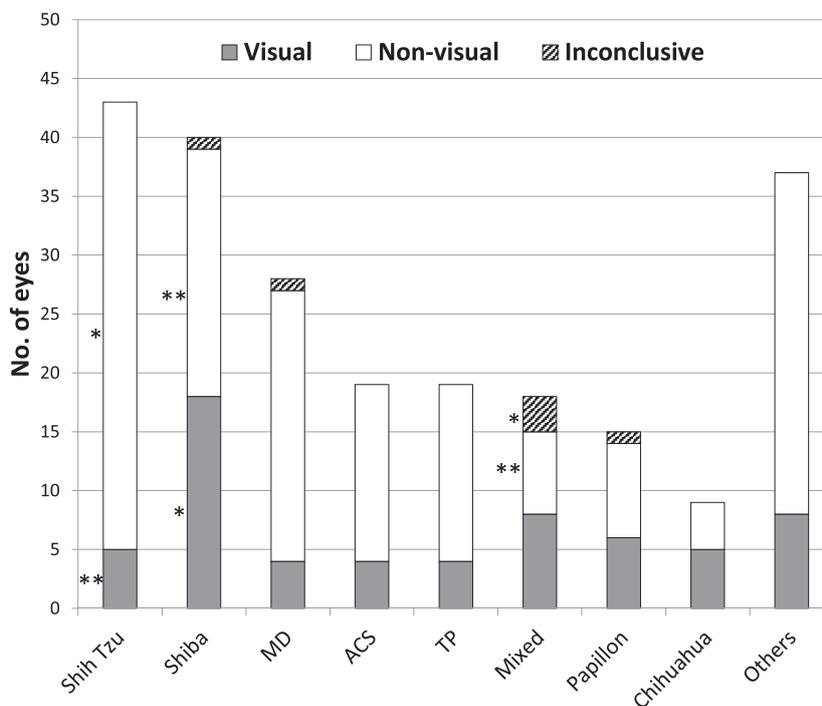


Fig. 4. Vision status at the first presentation in each breed group. Among breeds studied, Shiba was most likely visual, whereas Shih Tzu was least visual. In mixed-breed dogs, vision status was more likely inconclusive and less likely nonvisual at the time of first presentation. ACS: American Cocker Spaniel; MD: Miniature Dachshund; TP: Toy Poodle. Single asterisk (*) indicates significant overrepresentation, and double asterisks (**) indicate significant underrepresentation when compared to other groups of breeds by contingency table analysis ($P < 0.05$).

glaucoma cases of undermined cause (2 eyes/2 dogs) from 62 eyes of 60 dogs that were visual at the time of first presentation, vision outcome was compared between medical therapy (52 eyes of 50 dogs including 27 eyes/25 dogs with primary glaucoma and 25 eyes/25 dogs with secondary glaucoma) and AGV therapy (8 eyes of 8 dogs including 7 eyes/7 dogs with primary glaucoma, 1 eye/1 dog with glaucoma secondary to cataract surgery). The Kaplan-Meier (KM) curve showed that vision was maintained at significantly higher rates in the AGV group compared to the pharmacologically treated group (Fig. 5). The median time to vision loss was 9.9 weeks with medical treatment and 76.4 weeks with the AGV procedure. In dogs that underwent the AGV procedure, 6/8 eyes (75.0%) retained vision for at least 13 weeks, and 5 eyes (62.5%) for at least a year. By medical therapy, vision was maintained for 13 weeks or longer in 13 eyes (25.0%), 26 weeks or longer in 8 eyes (15.4%) and 1 year or

longer in 4 eyes (7.7%) after the initiation of the therapy.

Next, vision outcome was compared among 52 eyes of 50 dogs that received medical therapy by type of glaucoma, sex and breed. Primary glaucomas showed a KM curve similar to that of secondary glaucomas without any statistically significant difference (Fig. 6A). The median time to vision loss was 7.0 weeks for primary glaucoma and 11.0 weeks for secondary glaucoma. The KM curves were statistically similar for both sexes (Fig. 6B), and the median time to vision loss was 5.1 weeks for males and 17.7 weeks for females. The most represented breed in the medical therapy group was Shiba (15 eyes/14 dogs). Other breeds included were Papillon (6 eyes/6 dogs), Chihuahua (5 eyes/5 dogs), Miniature Dachshund (4 eyes/4 dogs), American Cocker Spaniel (4 eyes/4 dogs), Shih Tzu (3 eyes/3 dogs), Miniature Pinscher (2 eyes/2 dogs), and mixed breed (7 eyes/7 dogs). Toy Poodle, Cavalier King Charles

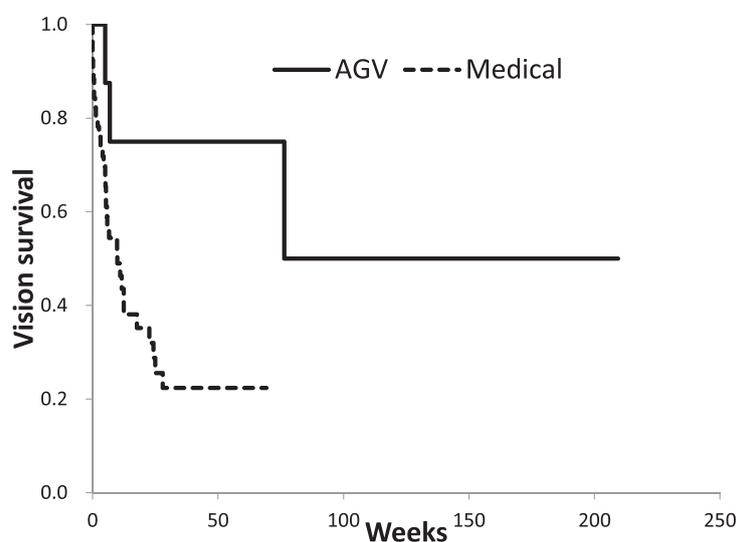


Fig. 5. Comparison of vision outcome by therapeutic modality. Vision was maintained at significantly higher rates after AGV placement compared to medical management. AGV: Ahmed glaucoma valve.

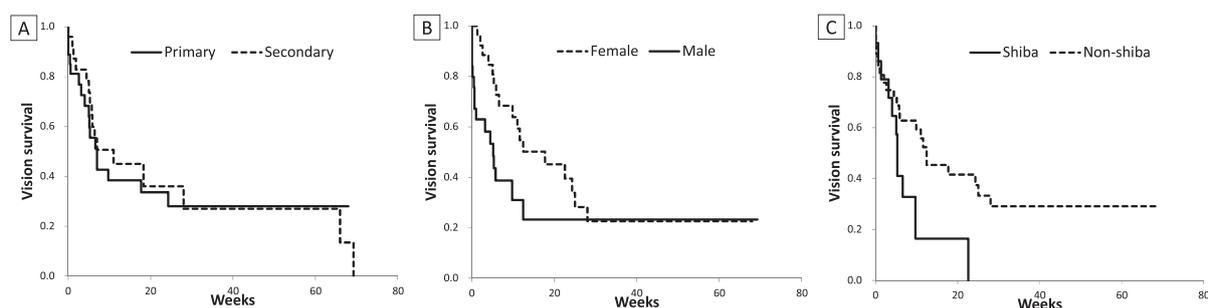


Fig. 6. Comparison of vision outcome under the medical therapy by type of glaucoma (A), between males and female (B) and between Shiba and non-Shiba dogs (C). A: The rate of vision survival was statistically similar between primary and secondary glaucomas. B: No significant difference was observed between males and females. C: The rate of visual preservation in Shiba dogs was significantly lower than other breeds of dogs combined.

Spaniel, Cairn Terrier, Border Collie, Maltese and Yorkshire Terrier were also in the group (1 eye/1 dog each). Vision outcome was compared between Shiba and non-Shiba dogs, because of the limited number of cases in breeds other than Shiba in the present study. The KM curve of Shiba dogs showed noticeably and significantly lower rates of vision retention throughout the study period (Fig. 6C). The medial time to vision loss was 5.3 weeks in Shiba and significantly shorter than 12.4 weeks in non-Shiba dogs. All Shiba dogs lost vision by 22.6 weeks after the initial presentation.

Discussion

The present study showed several distinctive epidemiological patterns of canine glaucoma compared to the previous studies reported in North America and other countries^{1,5,18-20} particularly in terms of breed and sex predilections. First, American Cocker Spaniel, Basset Hound, Wire Fox Terrier and Boston Terrier had a higher prevalence of primary glaucoma in the North American study⁵, but these breed predispositions were not observed in our study. The only breed that was significantly overrepresented was Shiba, and this result is consistent with the previous Japanese studies^{13,14}. Secondly, we found that the

cause of glaucoma was more likely inconclusive in Toy Poodle, but this breed is listed as one of the breeds of higher prevalence of primary glaucoma in the North American study. Thirdly, the secondary glaucomas investigated in the previous studies were often associated with cataract, uveitis and lens luxation^{6,12}. In our study, retinal detachment was also frequently present in addition to these conditions, and 14 of 25 eyes with retinal detachment were from Shih Tzu. In other words, 15 of 20 eyes of Shih Tzu dogs with secondary glaucoma had concurrent retinal detachment. This is probably because Shih Tzu is a popular breed in our country and it is the breed predisposed to retinal detachment¹⁰. Future studies would need to focus on the glaucomas of this breed. Lastly, it has been reported that female dogs are more affected by primary glaucoma in some breeds^{5,18}, but we did not see this effect, either. The prevalence was similar between females and males in all breeds investigated in the present study. These differences from overseas studies and similarity to other Japanese studies suggest that the epidemiology of canine glaucomas may be largely affected by breed preference, the environment and other regional factors.

Dogs with primary closed angle glaucoma are often presented with acute congestive glaucoma, and vision loss has been reported in nearly 50% of the cases at the time of first presentation and associated with poor response to medical therapy¹⁶. In a Japanese study¹¹, 73.3% of cases were presented within 3 days of onset, and vision was maintained in 54.5% of those cases presented within 3 days; after 4 days of onset, the vision survival rapidly and markedly declined to 8.9%. Compared to these reports, the percentage of visual eyes at the first presentation was considerably lower in our study (27.2%). This is partly because our center is a referral clinic and all patients were referred to us after consultation with their primary care veterinarians. The results of our study and others together underline the importance of education and raising awareness of

glaucoma as a potentially blinding eye disease that requires urgent care and should be preferably treated at the earliest stage possible before vision loss.

In our study, vision was maintained at a higher rate at the time of initial presentation in dogs with primary glaucoma than those with secondary glaucoma or glaucoma of unknown etiology. This is likely related to the high prevalence of Shiba in primary glaucoma and the high rate of visual eyes in this breed at the time of first presentation. Although the time to first presentation after onset was not studied, the glaucomas of Shiba are more easily recognized by the owners, because they often suffers from primary angle-closure glaucoma¹⁴, which causes acute congestion and severe pain in the early stage. In contrast, Shih Tzu was more frequently nonvisual at the time of initial consultation in our study. More than 50% of Shih Tzu dogs had secondary glaucoma, and concurrent retinal detachment was present in many of these cases. It is possible that these dogs had lost vision due to retinal detachment by the time of diagnosis of secondary glaucoma resulting in less visual patients at the time of first presentation.

Recent developments in new surgical technologies have widened options for antiglaucoma surgery. Consequently, successful vision outcome and IOP control have been reported for canine glaucomas in various studies^{2,3,7,8,9,21}. However, these studies primarily report post-surgical outcomes without any comparison with medical treatment alone. One reason for this is the complexity of factors involved in medical antiglaucoma treatment which is typically multimodal and consists of several different classes of drugs. In our study, however, the study population was divided into two basic groups with or without surgery to simplify the comparison. Although the number of cases that were visual at the time of initial presentation was limited in dogs that underwent the AGV implantation, the statistical analysis showed that vision outcome of AGV implantation was superior to that of

medical therapy alone. The shorter median vision survival of 9.6 weeks and progressive loss of vision over time in the medical treatment group support that prolonging vision by medical therapy alone is indeed very difficult. For long-term vision preservation, therefore, more proactive interventions including AGV implants should be considered, if patients are suitable candidates for antiglaucoma surgery. The data obtained in our study adds to the information that should be provided to owners to make an informed decision.

We also analyzed the effect of type of glaucoma, sex and breed on the vision outcome of dogs that were treated medically. To our knowledge, this type of study has not been reported before, and the results of our study provide a new reference for all future studies for comparison. We found that, contrary to the previous reports that showed more rapid vision loss in primary glaucoma than in secondary glaucoma^{11,16}, the vision outcome was similar between primary and secondary glaucomas that were treated medically in our study. With regard to a dog breed, Shiba was particularly overrepresented in medically treated glaucomas. Statistical comparison between Shiba and non-Shiba dogs showed a poorer vision outcome in Shiba. Shiba had significantly lower rates of vision survival compared to non-Shiba dogs, and all Shiba dogs eventually lost vision. The results of the study collectively indicate a clear predisposition to primary glaucoma and poorer vision outcome in Shiba, if treated medically, despite the high rates of retained vision at the first presentation. Hence, AGV implants or other aggressive options should be sought in this breed for better vision preservation.

The present study is limited by its retrospective design firstly, as with all other studies, and by the fact that it was conducted at a referral ophthalmology practice secondly. Thirdly, the results of the present study may reflect possible regional variations such as preferred dog breeds, and different results may be obtained in

other parts of the country. A nationwide study is needed to confirm or rule out this possibility. In the medical treatment of canine glaucoma, a wide array of drugs is used to preserve vision. Various pharmacological regimens, routes and dosages used were the fourth limitation of this retrospective study. Well-controlled future studies in a prospective design are needed to overcome this limitation.

In conclusion, AGV implants result in better vision outcome compared to medical therapy alone and should be considered in dogs that are visual at the time of presentation and suitable for surgery. And Shiba dogs are considered as the factor that indicate poor vision outcome of medical treatment alone in the present study.

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