Clinical Case Reports

Open Access

CASE REPORT

Surgical and medical treatment of ocular disease in a dog with Ehlers–Danlos syndrome

Søren N. Rasch

AniCura Århus Dyrehospital, Hasselager Centervej 12, Viby J 8260, Denmark

Correspondence
Søren N. Rasch, AniCura Århus Dyrehospital, Hasselager Centervej 12, 8260 Viby J, Denmark. Tel: +45 86 28 27 88; Fax: + 45 86 28 80 80; E-mail: soeren_rasch@hotmail.com

Funding Information
No sources of funding were declared for this study.

Received: 12 June 2016; Revised: 22 November 2016; Accepted: 5 March 2017

***Clinical Case Reports* 2017; 5(6): 880–886**

doi: 10.1002/ccr3.953

Key Clinical Message

Correctional surgery was performed on a 3-year-old intact male shih tzu presenting with Ehlers–Danlos syndrome, ocular disease, and skin fold dermatitis. A one-year follow-up showed that no further clinical corrections were needed. Therefore, surgery could be considered in some canine patients with Ehlers–Danlos syndrome.

Keywords

cutaneous asthenia, Ehlers–Danlos, Ehlers–Danlos syndrome, KCS, keratoconjunctivitis sicca

Introduction

Ehlers–Danlos syndrome (EDS), also called cutaneous asthenia [1, 2], is an uncommon connective tissue disease characterized by abnormal collagen structure in dogs. EDS inheritance in dogs is autosomal dominant [1, 3], but recessive forms have been postulated [3] and most frequently seen in Dachshunds, Boxers, St. Bernards, German Shepherds, Springer Spaniels, Greyhounds, Irish setters, and Poodles [4]. In cats, autosomal dominant and recessive inheritance is described [4] especially in Himalayans and Burmese [5–7]. In humans, at least six different subtypes are classified along with several examples of unclassified variants and overlapping phenotypes [8]. The syndrome is characterized by hyperextensibility and easily tearing skin due to collagen dysplasia and joint laxity, although it is rare to see both abnormalities present in dogs [2]. Skin tensile strength of dogs with EDS may be as low as 1/27 of normal dog skin [9]. Treatment and survival of dogs and cats with EDS differ as some are euthanized due to continuous skin tearing, whereas others have a reasonable quality of life but are best managed in a controlled environment [6, 7, 10]. The syndrome has been described in several other species including rabbit, cat, mink, sheep, cattle, and horse [2, 3, 11] although only a few publications describe abnormalities of the eye globe and surrounding tissues. Lens luxation, lens coloboma, diffuse cataractous changes, corneal pigmentation, corneal edema, and poor pupillary light reflex have been reported in one canine case, [2] but so far, no adnexal malformations except for palpebral hyperelasticity have been described in dogs with EDS. Medical treatment of a corneal ulcer using topical antibiotics was successful in one dog [2]; the same dog subsequently underwent a lens extraction procedure but was euthanized 2 days later due to poor prognosis of regaining vision and postoperative complications. However, wound healing of cornea and palpebral skin appeared normal within the time range. Skin wound healing in patients with EDS is reported normal in cats with EDS but variable in canine EDS patients [3, 12]. Vascular abnormalities are well described in humans but only once in dogs [13].

Only in human patients with EDS, ocular disease lens opacities, lens subluxation, decreased tear film breakup time and Schirmer's tear test 1 (STT-1) values, pathologic myopia, strabismus, microcornea, keratoconus, angioid streaks, abnormal vitreous, conjunctivochalasis, thin sclera, scleral staphyloma, retinal vessel abnormalities, and retinal detachment are described [1, 8, 14–16].

Case Report

Case history

A 3-year-old intact male shih tzu was referred to the clinic from a companion animal clinic due to ocular disease. The referring veterinarian had diagnosed the dog with EDS based on an extensibility index of 26.5% [1] and histopathology showing dermal collagen abnormalities supporting the clinical diagnosis. The referring vet had diagnosed KCS based on low STT values and thick mucoid discharge from the eyes as well as cherry eyes and entropion. According to the breeder of the dog, there was no known family history of similar skin problems. The referring veterinarian had performed previous surgical corrections of this patient's skin folds, and wound healing was reported normal.

A Nordic eye scheme examiner and the author performed the initial eye examination together, while only the author performed follow-up examinations. The initial ophthalmic examination was performed using slit lamp biomicroscopy (Kowa SL-14; Kowa Optimed Inc., Torrance, CA). The dog presented with blinding superficial pigmentary keratitis (Fig. 1.), bilateral prolapse of the third eyelid glands (Fig. 2), and pronounced bilateral entropion of the superior palpebrae due to excessive amounts of skin on the forehead. A slight entropion was noted on the medial one-third of the left inferior palpebra. On the entire right inferior palpebra, subtle entropion was noted in the middle of the eyelid. Hyperelasticity of the eyelids as well as blepharitis secondary to the constant moisture of the eyelids was present.

Figure 1. Notice the massive pigmentary keratitis and blepharitis secondary to wetting of the eyelids were present. The prolapsed gland of the third eyelid has been manually repositioned prior to photographing.

Figure 2. Prolapsed gland of the third eyelid as well as entropion of the superior eyelid.

Pupillary light reflexes or other visual examinations of the internal structures of the eye globe could not be evaluated, due to dense bilateral pigmentation and some vascularization of the cornea. Dazzle response was present bilaterally. There was neither menace response nor response to the falling cotton ball test. The dog also occasionally bumped into objects in the consultation room.

Mucoid, yellowish discharge was present bilaterally, and insufficient tear production was confirmed using STT-1 (Tearex, Dioptrix, Toulouse, France) measuring 8 and 7 mm on the right and left eye, respectively. Fluorescein staining was negative bilaterally (Bio Glo, Rose Stone Enterprises, Alta Loma, CA). Tonometry showed an intraocular pressure of 18 mmHg on right eye and 16 mmHg on the left eye using rebound tonometry (TonoVet, Icare Finland Oy). The corneas were locally anesthetized using a drop of topical oxybuprocaine (oxybuprocaine hydrochloride 0.4% w/v eyedrops, Bausch & Lomb, Aubenas, France), and an ultrasonography scanning of the eye globes was performed; this revealed no abnormalities (290178 MyLab 30 Vet scanner, microconvex array probe CA 123 14 mm 3–9 MHz, Esaote).

On the general health check, severe dermatitis was noticed perianally and on the caudal areas of the hind limbs due to excessive skin folding causing serious welfare issues for the dog. No other abnormalities were found while performing the general health check. The patient was up to date with relevant vaccinations used in Denmark. It is uncertain whether the abnormalities were noticed earlier, as the present owners had only had the dog for 3 months before presentation at the referring

veterinarian, and the previous owners could not be contacted.

Preoperative considerations

Correction of the skin folds of the perianal area was the first priority, as skin fold dermatitis was assessed to be the most urgent welfare issue. In order to avoid prolonged anesthesia, it was decided to perform the surgery over two sessions.

During the first surgery, the skin folds were corrected on the lumbar area and hind limbs, the prolapsed third eyelid glands, and the ventral entropion. The dorsal entropion was addressed temporarily using tacking sutures. Stade's forced-granulation procedure and a stellate rhytidectomy procedure were performed 2 weeks later.

As severe side effects to normal preparation with dilute povidone–iodine solution have been described in a dog with EDS, it was decided to use another protocol for surgical site preparation. Due to very limited finances of the owner and that the dog had surgery before without complications, no CBC or biochemistry was performed.

Preoperative preparation

The dog was sedated with an intramuscular injection (IM) of medetomidine (36.7 μg/kg, Sedastart, Scanimal, Oudewater, Holland) and butorphanol (0.1 mg/kg, Torbugesic Vet; ScanVet Animal Health, Fredensborg, Denmark). The epiglottis was anesthetized with a dose of Xylocaine spray (lidocaine 10 mg/dose, AstraZeneca, Luton, Bedfordshire, United Kingdom), and afterward, a tracheal tube was placed. Anesthesia was maintained using isoflurane (Vetflurane, 1000 mg/g, Virbac, Carros, France) and oxygen. Meloxicam 0.2 mg/kg (Metacam, Boehringer Ingelheim, Ingelheim am Rhein, Germany) was given subcutaneously (SC) just prior to the surgical procedures.

The surgical area on the lumbar and lateral parts of the hind legs was prepared using clippers (Isis GT420, Aesculap, B. Braun Vet Care GmbH, Melsungen, Germany), washing with skin scrub solution (Dermastel PHMB, Tristel Solutions Limited, Cambridgeshire, United Kingdom) and finally chlorhexidine ethanol (Ceduren, Kemex A/S, Silkeborg, Denmark). The same procedure was performed to prepare the skin of the eyelids for the surgical procedure. To protect the corneal surface from any surgical scrub, a large amount of eye lubricant (Lubrithal, Dechra Veterinary Products A/S, Uldum, Denmark) was used and afterward it was rinsed thoroughly with sterile isotonic NaCl solution. A couple of small abrasions occurred while clipping the hairs on the eyelids as the skin was fragile.

Surgical procedure

A 35–cm-long and 13-cm-wide skin incision over the back and lumbar area was made as well as 7-cm-wide skin flaps over the hind legs (Fig. 3) using a no. 24 scalpel (Aesculap AG, Tuttlingen, Germany). The skin was loosened using blunt dissection with pair of curved Mayo scissors. Subsequently, the skin edges were apposed and sutured with two layers, the first layer using a continuous suture pattern and a 3-0 vicryl suture (Ethicon, Johnson & Johnson, New Brunswick, NJ), the second using an interrupted suture pattern and Prolene suture 3-0 (Ethicon, Johnson & Johnson).

The pocket technique was used for replacing the prolapsed third eyelid gland. The eyes were rinsed with a sterile isotonic NaCl solution prior to the surgical procedure. A scalpel blade no. 15 was used to make two parallel incisions dorsally and ventrally to the prolapsed glands on the bulbar conjunctiva. The glands were repositioned, and the margins of the incisions were sutured using a continuous pattern with vicryl 5-0 (Ethicon, Johnson &

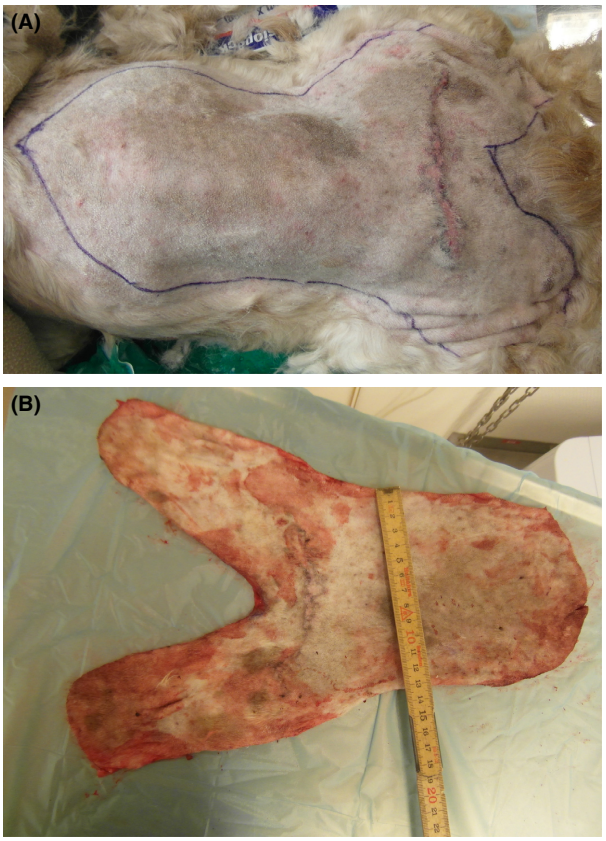

Figure 3. (A) Outline of the area to be resected marked during preparation for the resection of skin over the back of the patient. (B) The resected area of skin after surgery.

Johnson) with anchoring of the knots on the anterior surface of the third eyelid (Fig. 4).

Celsus–Hotz procedure was used for correcting the inferior eyelid entropion. Using a Braun BB 365 R scalpel (B. Braun, Aesculap AG, Tuttlingen, Germany), skin incisions were made approximately 3 mm from and parallel to the eyelid margin. A small tear of the skin occurred in the medial part of the incision as the skin was fragile. A skin strip 1–2 mm wide was then freed using a pair of curved mayo scissors for blunt dissection. The margins of the incisions were then reappositioned and sutured with a simple interrupted suture pattern using vicryl 5-0.

Afterward, three tacking sutures were placed in the superior eyelids using Prolene 3-0. Noticeably, very little hemorrhaging occurred during all these procedures.

To reverse the effect of the medetomidine, an IM dose of 183.5 μg/kg atipamezole was given (Sedastop, Scanimal, Oudewater, Holland). When the dog had recovered from the anesthesia, tissue swelling was evaluated and was found not to be excessive compared to patients without EDS.

Fluorescein staining of the cornea was repeated and found negative.

Chloramphenicol and dexamethasone (Spersadex comp, 1/5 mg/mL, Laboratoires THEA, Clermont-Ferrand Cedex, France) eyedrops were prescribed four times daily for 3 weeks to minimize inflammation and treat current conjunctivitis. Cyclosporine A (2 mg/g, Optimmune, Intervet International BV, Boxmeer, Holland) eye ointment was prescribed two times daily to increase tear production. Systemic antibiotic and analgesic treatment for 10 days using cefadroxil 100 mg two times daily orally (Cefa-Cure Vet, Intervet International BV, Boxmeer, Holland) and meloxicam 0.1 mg/kg one time daily (Metacam oral solution, 1.5 mg/mL, Boehringer Ingelheim, Ingelheim am Rhein, Germany) was initiated.

Figure 4. Appearance of the patient immediately postsurgery involving replacing the third eyelid gland using the pocket technique, correction of medial entropion using Celsus–Hotz technique, and eyelid tacking of the upper eyelid.

Fourteen days after the first surgery, the dog came in for the final surgery. On the checkup prior to surgery, the dog had regained some vision; dazzle reflex, menace response and falling cotton ball responses were positive. Furthermore, the owner had noticed that the dog had stopped bumping into obstacles. Pigmentation of the corneas appeared to be breaking up but deemed not sufficient to warrant examination of the intraocular structures using slit lamp biomicroscopy.

SST-1 values were 18 mm on the right eye and 13 mm the left eye. IOP was 17 and 16 mmHg on right and left eye, respectively. The tacking sutures had pulled through the skin so the entropion on the superior palpebrae returned to their preoperative state. The perianal dermatitis was under control so no further correction was needed in this area.

The dog was anesthetized, and surgical areas were prepared according to the same protocol as previously used. First, the stellate rhytidectomy procedure on the skin of the dog's forehead was performed using a scalpel blade no. 15 for the skin incisions, and the skin was loosened using blunt dissection with a pair of curved mayo scissors. The cutis and subcutis was sutured in two layers, first a simple continuous suture pattern using vicryl 3-0 for the subcutaneous layer, then a simple interrupted suture pattern for the cutis using Prolene 3-0. Afterward, a Stade's forced-granulation procedure was performed bilaterally using a scalpel no. 15 to make an incision of 0.5 mm from and parallel to the lid margin and a 2.5-cm crescent-shaped incision on the palpebrae. Vicryl 5-0 was used to suture the skin margins approximately 5 mm from the lid margins. On checkup 5 days postsurgery, the wound edges were healing by secondary granulation.

Over the next 12 months, the dog was examined 12 times using slit lamp biomicroscopy, measuring tear production and IOP. Furthermore, menace response and falling cotton ball tests were performed. The STT-1 values were within the normal range (15–25 mm) for 4 months for both eyes, but then began to decrease on the right eye and after 6 months were at 3–4 mm.

The first 2 months postsurgery, some of the pigmentation of the corneas slightly broke up, but not enough to warrant examination of the lens or the fundus (Fig. 5). However, as the STT values dropped on the right eye, pigmentation increased and menace response was negative in the eye in spite of treatment with lubricating drops three times daily (Sentrx Eye Drops, Orion Pharma, Espoo, Finland) and cyclosporine two times daily. During the time of the study, pigmentation of the left cornea did

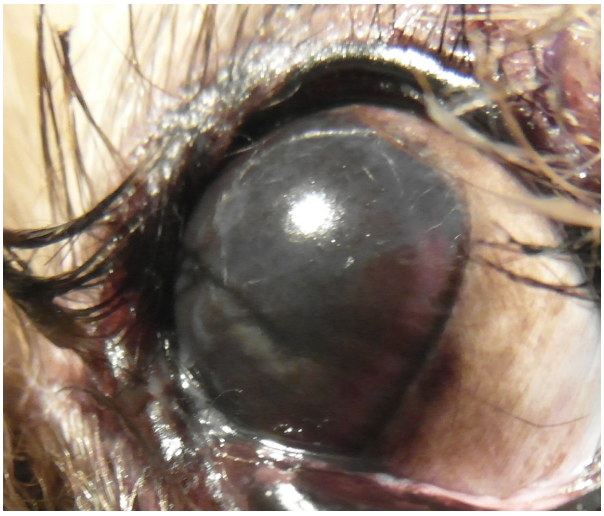

Figure 5. Slight breakup of pigment in the cornea of the left eye nearly 4 months after the first surgery but not sufficiently to allow a good examination of the internal structures of the eye. Small areas of iris can be seen, especially near limbus.

not break up any further. Menace response and falling cotton ball response were still intact on this eye at the end of the study (Fig. 6).

Discussion

To the author's knowledge, this is the first description of surgical and medical treatment of ocular disease in a dog with EDS and long-term follow-up. Some vision was regained in the left eye, although pigmentation of the left cornea did still not allow the dog to have normal vision

Figure 6. Appearance of the eyelids 2 months after the last surgery was shown.

on the eye. But the overall objective of regaining vision and increasing ocular comfort was achieved. Keratoconjunctivitis sicca unresponsive to treatment with cyclosporine A responds to treatment with tacrolimus or pimecrolimus in most cases [17–19], so the possibility to treat the right eye was investigated. However, no approved eye formulations are available on the Danish market, and pharmacies were not able to obtain tacrolimus to produce a compounded formulation for ocular use. Permission to import tacrolimus eye formulations was denied by the Danish Pharmacy Board. Parotid duct transposition was not performed as the risk of complications was too high when handling the fragile tissues. Furthermore, the owner was satisfied with the results from the initial treatments and disliked the adverse effects of parotid duct transposition.

Although this patient was followed for 12 months and did not show signs of requiring further surgery, it cannot be ruled out that further corrections would be needed later on. It is unclear whether other cases of surgical treatment of EDS would be able to respond as favorably as this one did as no further pathophysiological subtyping of the EDS was performed. This case does show though promising results for surgical skin corrections in canine patients with EDS.

Most cases of EDS are presented before the age of 1 year [1–3, 20, 21] although some may present at a later age. It cannot be determined whether the dog has previously been affected by the disease as it was not possible to get in contact with the previous owner of the dog.

The canine case described by Barnett & Cottrel experienced postsurgical complications after a lens extraction. Severe chemosis occurred as the dog had the eye prepared for surgery with dilute povidone–iodine solution. They described normal wound healing of the skin, but the patient was euthanized 2 days postsurgery due to chemosis, exophthalmos, pain, and poor prognosis of regaining vision. This may be ascribed to the fact that the dog had both ocular signs of EDS and joint laxity and therefore may represent another subtype of EDS combined with a more invasive procedure. In the present case, no abnormal chemosis was noted after correcting the prolapsed third eyelid glands. As povidone–iodine solution was not used, it is uncertain whether a similar reaction would occur in this case. Before surgery, investigation into recurrence of the prolapsed third eyelid glands was made as this occurs [22–24] but this patient had no complications. To the author's knowledge, cherry eye has not been described in canine EDS patients. Cherry eye is seen in many breeds [23] including the shih tzu and is believed to be inherited but the mode of inheritance is unknown [25]. In dogs with EDS, the weakening of the connective tissue may predispose to cherry eye although in this case,

it could not be determined whether it was secondary to EDS.

In conclusion, this case shows that surgical and medical treatment can be viable in a one-year follow-up study in improving vision and general quality of life in a canine EDS patient. To the author's knowledge, this is the first case describing cherry eye and surgical correction in a dog with EDS.

Acknowledgments

The author would like to thank Susanne Kaarsholm, DVM, Nordic eye scheme examiner, for examining the dog with the author and planning the treatment, and Kerstin Halberg, DVM, for referral of the patient and initial diagnostic workup of the patient. Furthermore, thanks to Dr. Ann Refstrup Strom, Dipl. ACVO, for inputs and editing.

Conflict of Interest

None declared.

Authorship

SNR: contributed to the clinical work and writing this case report.

References

1. Matthews, B. R., and G. T. Lewis. 1990. Ehlers-Danlos syndrome in a dog. Can. Vet. J. 31:389–390.
2. Barnett, K. C., and B. D. Cottrell. 1987. Ehlers-Danlos syndrome in a dog: ocular, cutaneous and articular abnormalities. J. Small Anim. Pract. 28:941–946.
3. Paciello, O., F. Lamagna, B. Lamagna, and S. Papparella. 2003. Ehlers-Danlos-like syndrome in 2 dogs: clinical, histologic, and ultrastructural findings. Vet. Clin. Pathol. 1:13–18.
4. Bellini, M. H., E. T. E. G. Caldini, M. P. Scapinelli, M. J. Simões, D. B. MacHado, and R. Nürmberg. 2009. Increased elastic microfibrils and thickening of fibroblastic nuclear lamina in canine cutaneous asthenia. Vet. Dermatol. 20:139–143.
5. Counts, D. F. 1980. Isolation of collagen from the skins of Ehlers-Danlos syndrome-affected dogs by acetic acid extraction and pepsin digestion. Biochim. Biophy. Acta 626:208–217.
6. Holbrook, K. A., P. H. Byers, D. F. Counts, and G. A. Hegreberg. 1980. Dermatosparaxis in a Himalayan Cat: II: Ultrastructural Studies of Dermal Collagen. J. Invest. Dermatol. 74:100–104.
7. Hansen, N., S. F. Foster, A. K. Burrows, J. Mackie, and R. Malik. 2015. Cutaneous asthenia (Ehlers-Danlos-like syndrome) of Burmese cats. J. Feline Med. Surg. 17:954–963.
8. Whitaker, J. K., P. Alexander, D. Y. Chau, and N. L. Tint. 2012. Severe conjunctivochalasis in association with classic type Ehlers-Danlos syndrome. BMC Ophthalmol. 12:47.
9. Hegreberg, G. A., G. A. Padgett, R. L. Ott, et al. 1970. A heritable connective tissue disease of dogs and mink resembling Ehlers-Danlos syndrome of man. J. Invest. Dermatol. 54:377–380.
10. Dokuzeylül, B., E. D. Altun, and T. H. Özdoğan. 2013. Cutaneous asthenia (Ehlers – Danlos syndrome) in a cat. Turkish J. Vet. Anim. Sci. 37:245–249.
11. Sinke, J. D., J. E. van Dijk, and T. Willemse. 1997. A case of Ehlers-Danlos-like syndrome in a rabbit with a review of the disease in other species. Vet. Q. 19:182–185.
12. Freeman, L. J., A. G. Hegreberg, and J. D. Robinette. 1989. Cutaneous wound healing in Ehlers-Danlos syndrome. Vet. Surg. 18:88–96.
13. Uri, M., R. Verin, L. Ressel, L. Buckley, and N. McEwan. 2015. Ehlers-Danlos syndrome associated with fatal spontaneous vascular rupture in a dog. J. Comp. Pathol. 152:211–216.
14. Gharbiya, M., A. Moramarco, M. Castori, F. Parisi, C. Celetti, M. Marenco, et al. 2012. Ocular features in joint hypermobility syndrome/ehlers-danlos syndrome hypermobility type: a clinical and in vivo confocal microscopy study. Am. J. Ophthalmol. 154:593–600.
15. Nakazawa, M., M. Tamai, M. Kiyosawa, and Y. Watanabe. 1986. Homograft of preserved sclera for post-traumatic scleral staphyloma in Ehlers-Danlos syndrome. Graefes Arch. Clin. Exp. Ophthalmol. 224:247–250.
16. Chikamoto, N., S. Teranishi, T. Chikama, T. Nishida, K. Ohshima, and Y. Hatsukawa. 2007. Abnormal retinal blood vessels in Ehlers-Danlos syndrome Type VI. Jpn. J. Ophthalmol. 51:453–455.
17. Berdoulay, A., R. V. English, and B. Nadelstein. 2005. Effect of topical 0.02% tacrolimus aqueous suspension on tear production in dogs with keratoconjunctivitis sicca. Vet. Ophthalmol. 8:225–232.
18. Hendrix, D. V. H., E. A. Adkins, D. A. Ward, J. Stuffle, and B. Skorobohach. 2011. An investigation comparing the efficacy of topical ocular application of tacrolimus and cyclosporine in dogs. Vet. Med. Int. 2011:487592.
19. Ofri, R., G. N. Lambrou, I. Allgoewer, U. Graenitz, T. M. Pena, B. M. Spiess, et al. 2009. Clinical evaluation of pimecrolimus eye drops for treatment of canine keratoconjunctivitis sicca: A comparison with cyclosporine A. Vet. J. 179:70–77.
20. Barrera, R., C. Mane, E. Duran, M. A. Vives, and C. Zaragoza. 2004. Ehlers-Danlos syndrome in a dog. Can. Vet. J. 45:355–356.
21. Rodriguez, F., P. Herráez, A. Espinosa de los Monteros, P. Calabuig, and J. L. Rodriguez. 1996. Collagen dysplasia in

a litter of Garafiano shepherd dogs. Zentralbl. Veterinarmed. A. 43:509–512.
22. Plummer, C. E., M. E. Källberg, K. N. Gelatt, K. P. Barrie, and D. E. Brooks. 2008. Intranictitans tacking for replacement of prolapsed gland of the third eyelid in dogs. Vet. Ophthalmol. 11:228–233.
23. Sapienza, J. S., A. Mayordomo, and A. M. Beyer. 2014. Suture anchor placement technique around the insertion of the ventral rectus muscle for the replacement of the prolapsed gland of the third eyelid in dogs: 100 dogs. Vet. Ophthalmol. 17:81–86.
24. Prémont, J. E., S. Monclin, F. Farnir, and M. Grauwels. 2012. Perilimbal pocket technique for surgical repositioning of prolapsed nictitans gland in dogs. Vet. Rec. 171:247.
25. Christmas, R. E. 1992. Common ocular problems of Shih Tzu dogs. Can. Vet. J. 33:390–393.