Persistent pupillary membranes in dogs and cats

Persistent pupillary membranes (PPMs) are embryonic residues of neural-crest origin. During the embryonic life, the pupillary membranes have the role of feeding the developing lens but they lose this function when the aqueous humour is produced. Normally, few weeks after birth, the pupillary membranes undergo atrophy. Alterations of this process and its continuous persistence are responsible of pathological events. The manifestations of PPMs vary from iris residues to fibrous filaments that attach to the lens or cornea (dysplastic pupillary membranes). For rare cases that need therapeutic intervention, medical therapy or, very rarely, surgery are required. The breeds mainly predisposed to this disease are for dogs: Basenji, Chow Chow, Petit Basset Griffon Vendeen, English Cocker Spaniel, while for cats: the Bengal, Birman and Persian. This article describes the clinical manifestations of PPM and the breeding advice in the different clinical conditions.

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DEFINITION, EMBRYOGENESIS AND HISTOLOGY

In human medicine the first authors who described an anomaly in the regression of embryonic vessels were Reese and Payne.[1]

Cibis described for the first time the persistence of pupillary membranes.[2] Goldberg reviewed the different manifestations of fetal vessel persistence in the anterior and posterior sectors of the eye and coined the general term «persistent fetal vasculature» (PFV).[3]

Pupillary membranes are vascular, connective, transient, non-pathological tissue, present during intrauterine development and originated from neural-crest (NC). The cells of the NC migrate from the neural tube and invade the primitive periocular region,[4] differentiating in all connective tissues of the eye (except for the vasal pericytes) contributing to the formation of the anterior tunica vasculosa lentis (TVL). The TVL has the trophic action of the embryonic lens.[5] Pupillary membranes are in communication with the minor arterial circle of the iris and tend to regress typically between 14 days post-birth or in rare occasions even post 6 months.[6] The persistence of pupillary membranes is therefore a neurocristopathy that falls within the mirror of anterior segment dysgenesis.[5] Several diseases have been associated with abnormal development of the NC and its derivatives. They are collectively known as neurocristopathies. These diseases can be the result of defects in NC specification, migration, proliferation, survival or differentiation.[4] In

Persistent pupillary membranes (PPMs) are embryonic residues that persist after losing their trophic lens function during intrauterine life.

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PPMs are a neurocristopathies. Histologically they consist of connective tissue, pigmented cells and leukocytes. Histological changes affect the endothelium (Descemet's membrane and stromal fibrosis) and the lens (sub capsular cataract, epithelial proliferation and capsular dysplasia).

PPMs there is a lack of involution of the vessels of the anterior tunica vasculosa lentis. The mechanisms of involution of this vascular system are not yet completely understood, but certainly the presence of macrophages plays an important role, in fact macrophages actively elicit cell death[7] Moreover, iris movements during development favour the migration of macrophages and apoptosis of the pupillary membranes. Mice with pharmacologically induced mydriasis were found to have persistence of pupillary membranes after birth.[8] Electron microscopy showed degeneration of fibroblasts and collagen fibrils, disruption of the tight junction of endothelial cells due to macrophagic activity and increased phagocytic activity.[9] During the process of involution, the fibroblasts proliferate impairing blood flow in vessels that become whitish and undergo atrophy.[10] The central vessels tend to regress earlier, while those near the collarette regress later.[11]

From a histological point of view, fetal pupillary membranes consist of endothelial cells, a thin basal membrane, pericytes, collagen fibrils and few fibroblasts; on the other hand, persistent pupillary membranes consist of connective tissue with pigmented cells and leukocytes.[10] Corneal adhesion of PPMs leads to focal endothelium absence, defects in Descemet's membrane and stromal fibrosis (fibrous metaplasia of the corneal endothelium); while the insertion of PPMs on the lens is responsible for sub capsular cataract associated with epithelial proliferation.[12]Iris atrophy and synechiae are the two major differential diagnoses that are differentiated both clinically and histologically by the loss of iris tissue in the former and broad iris attachments to the lens (posterior synechiae) and anterior synechiae in the latter.[13]

CLASSIFICATION AND CLINICAL MANIFESTATIONS AND BREEDING ADVICE

The incidence of PPMs is low and it is reported to be 0.7% in Beagle between 16-24 weeks.[14] PPMs have the same colour as the iris and they can be observed alone or in association with other MOA (multiple ocular anomalies).[13] In cats they can be observed in association with upper eyelid agenesis,[15] in dogs with congenital cataract in English Cocker Spaniel and in Chow Chow with cataract, entropion, nystagmus, microphthalmia and retinal dysplasia.[11] In human medicine the presence of PPM with total absence of the iris is very rare and is normally associated with multiple ocular anomalies (MOA).[16]

Duke-Elder has classified the vascular membranes remnants in different types:

- Type I are those present on the iris or that make contact with iris tissues;
- Type II are the iridous-lenticular adhesions;
- Type II sub-variant: only single or clumped stromal melanocytes, aberrantly located on the anterior capsule of the lens, are detected. These pigments are often called «chicken tracks»;
- Type III are membranes that attach to the cornea. In human medicine they are commonly found in Axenfeld-Rieger syndrome.[17]

Their incidence is 0.7% in Beagle. In cats they are commonly observed in association with eyelid agenesis, while in dogs with cataract in English Cocker Spaniel and in Chow Chow with cataract entropion, nystagmus, mycrophtalmia and retinal dysplasia.

This classification can also be easily adapted to veterinary medicine.

The persistence of pupillary membranes is clinically evident in several ways:

1. Presence of pigmented and/or fibrotic remnants on the anterior lens capsule: these normally manifest as multifocal spots to be distinguished from iris posterior synechiae pigment residues. They need evaluation for breeding advice purpose if considered obstructive at naked eye examination.[18,19]
   Breeding advice: The ECVO manual suggests: if the pigment in the anterior capsule is substantial NO BREEDING (in this case at naked eye examination is useful: if they are visible without magnification, they are considered substantial).
   Anyway, pigmented dots centrally on the anterior capsule of the lens are only reported in the certificate in the "drawing area" and are not ticked "undeter-

According to the Duke-Elder classification of vascular residues, PPMs are distinguished in: type I (contacts with only the iris); type II (irido-lenticular adhesions); type II sub-variant (pigment clumps localized in the anterior capsule of the lens); and type III (irido-corneal adhesions).

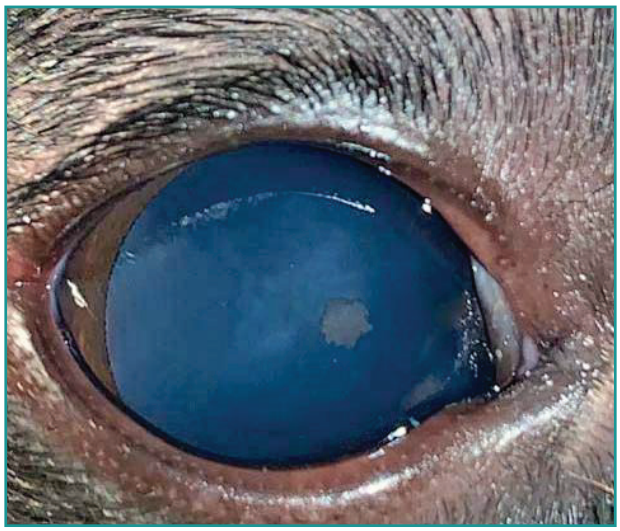

Figure 1 - Pigment clump attached to the lens (courtesy of dr. Francesca Corsi).

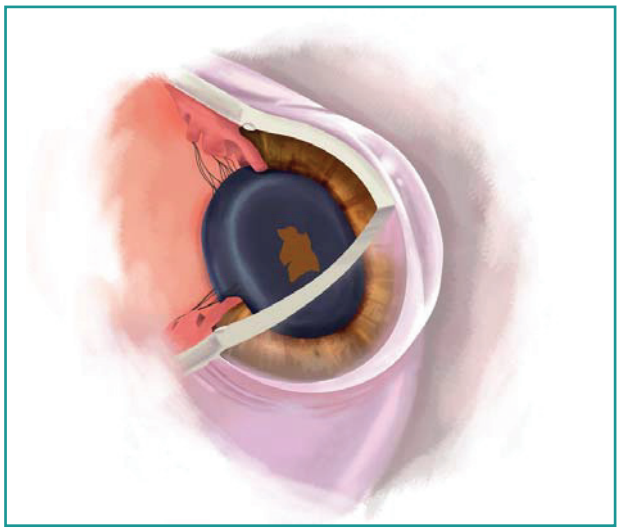

Figure 2 - Cartoon representation of pigment clump attached to the anterior capsule of the lens.

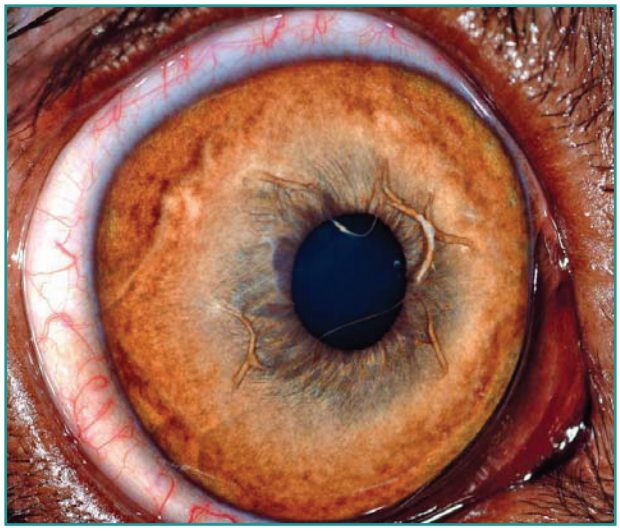

Figure 3 - PPM localized in the iris (courtesy of dr. John Sapienza).

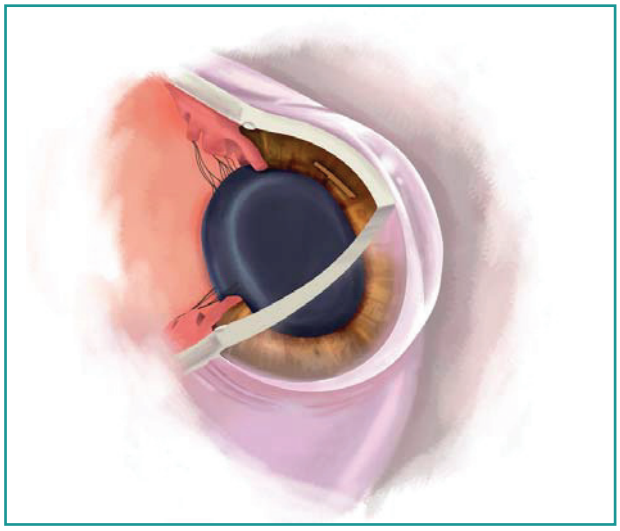

Figure 4 - Cartoon representation of PPM in the iris.

mined" or "affected" for PPM.[34] (Figures 1 and 2)

2. Presence of membranes on the iris: these can have different shapes, being single or multiple, and present as a Y or V shape with apex in the iris collarette. Their presence has moderate clinical significance but they can be a marker for monitoring the transmission of the pathology during breed selection[11] (Figure 3 and 4).
   Breeding advice: optional.[34]
3. Presence of iris-iris membranes: these are filaments of membranes that originate from one side of the collarette and attach to the opposite side while they are free floating in the central portion (Figures 5 and 6).
   Breeding advice: optional.[34]
4. Laminae: according to the classification included in the ECVO manual (hereditary eye disease manual of the European College of Veterinary Ophthalmologists) these are different filaments of membranes that tend to converge in axial position. In veterinary medicine the term «cob-web-like» or "spider web" of tissue is often used to indicate laminae while in human medicine the term «caput medusae» is used due to their similarity to the medusa head of classical iconography (Figures 7 and 8).
   Breeding advice: NO BREEDING from the affected animal.[34]
5. Iris-lens pupillary membranes: these are adhesions of the pupillary membranes with the lens. It is correct to define them as dysplastic pupillary membranes

Figure 5 - PPM iris to iris (courtesy of dr. Fausto Cucinotta).

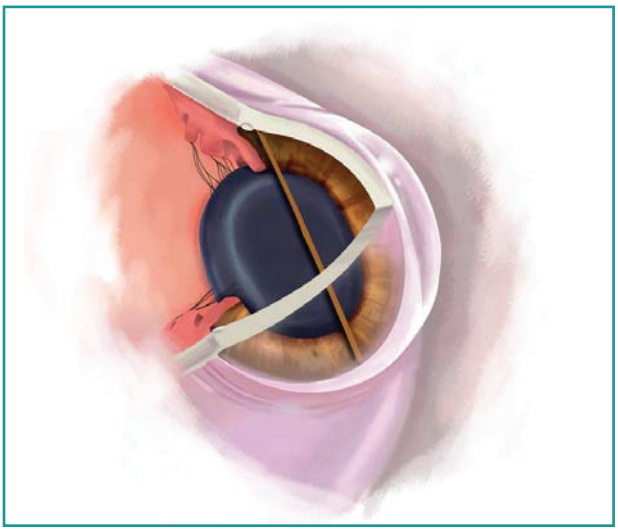

Figure 6 - Cartoon representation of PPM iris to iris with free floating in the central position.

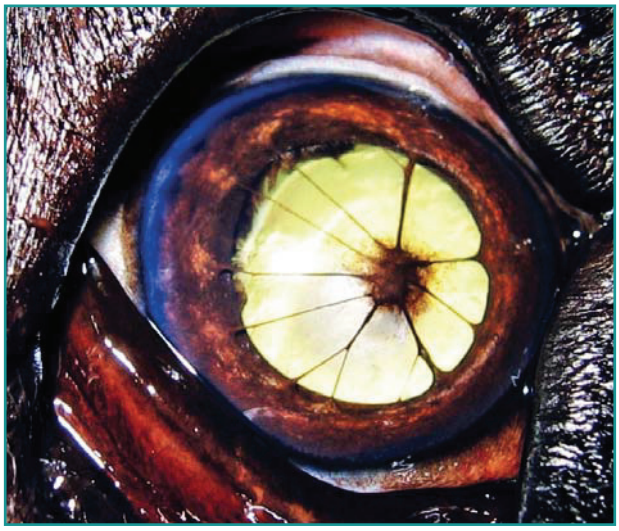

Figure 7 - Multiple ocular anomaly with PPM laminae, (courtesy of dr. Nunzio d'Anna).

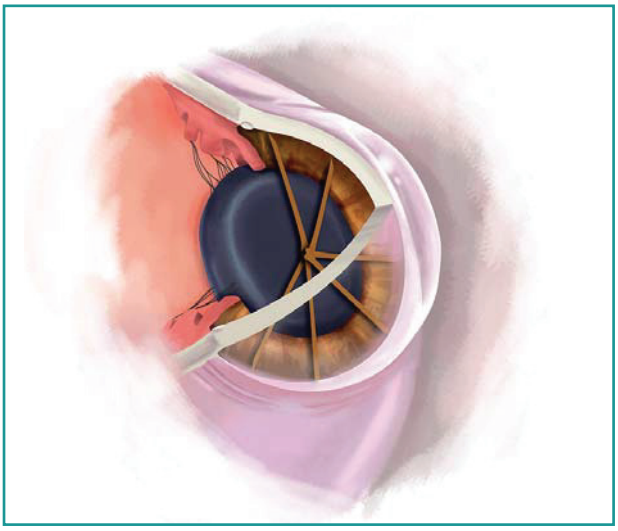

Figure 8 - Cartoon representation of "spider web", "cob-web-like" laminae.

(DPM) rather than persistent membranes. The contact between the pupil membrane and the anterior lens capsule is responsible for proliferation and dysplasia of the lenticular epithelium and therefore cataract (Figures 9 and 10).[12]
Breeding advice: NO BREEDING from the affected animal.[34]

PPMs are membranes that can be found in the iris or in contact with the cornea and lens and give different clinical manifestations. Breeding recommendations: no breeding for animals with DPM iris to cornea, DPM iris to lens, with laminae and for animals with corneal fibrosis and lens pigment visible with the naked eye examination.

6. Iris-corneal pupillary membranes: these are always indicated as DPM and are adhesions of the pupil membranes with the corneal endothelium. They are responsible for fibrous metaplasia of the endothelium that results in an adherent leukoma. Occasionally, a perilesional edema may be found. The lesions on the cornea may appear point-like with linear or circular shape and white or brownish coloured (Figures 11 and 12).
   Breeding advice: NO BREEDING from the affected animal.[34]
7. Endothelial fibroplasia: this can be found in some cases also in absence of visible pupillary membranes. They can be examined by bio-microscopy as localized endothelial or posterior stromal lesions. (Figures 13 and 14).
   Breeding advice: according to the ECVO manual if

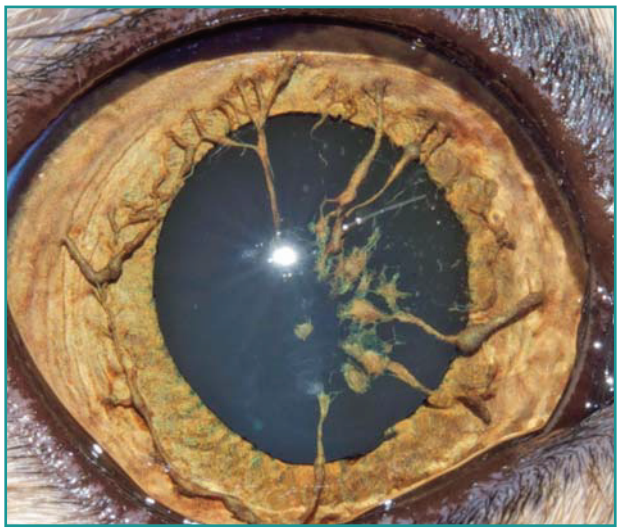

Figure 9 - Iris to lens DPM in a dog (courtesy of dr. Mario Vergara).

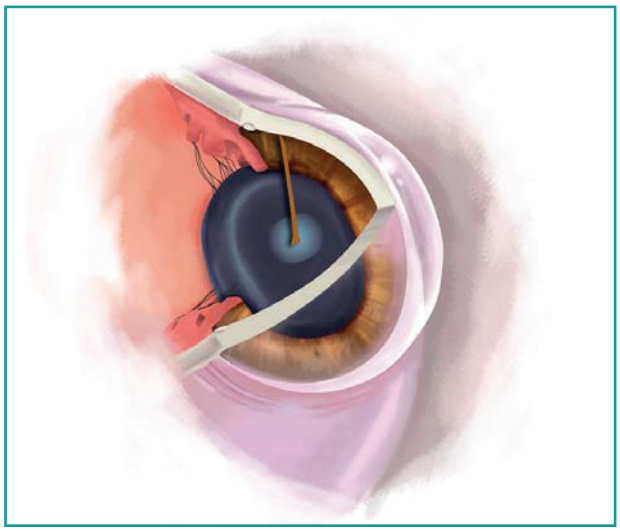

Figure 10 - Cartoon representation of DPM iris to lens.

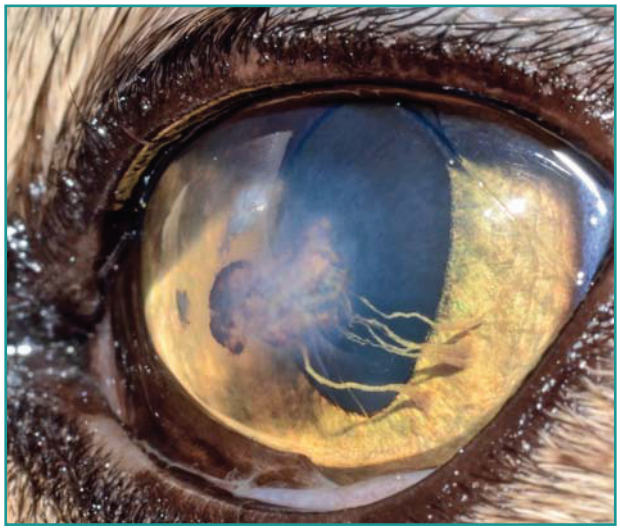

Figure 11 - DPM iris to cornea with adherent leukoma in a cat (courtesy of dr. Mario Vergara).

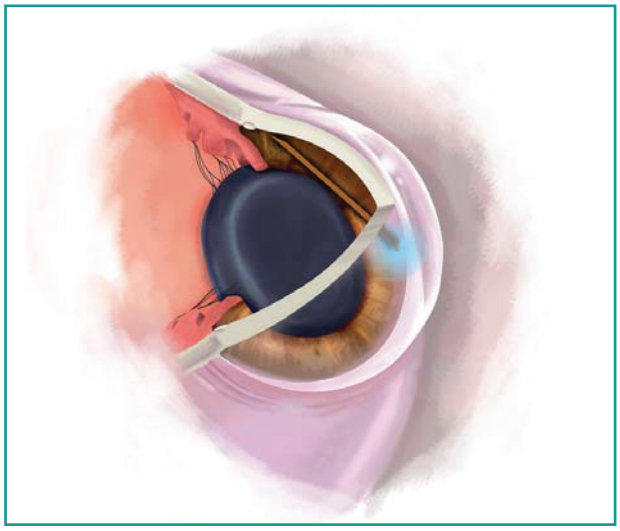

Figure 12 - Cartoon representation of DPM iris to cornea.

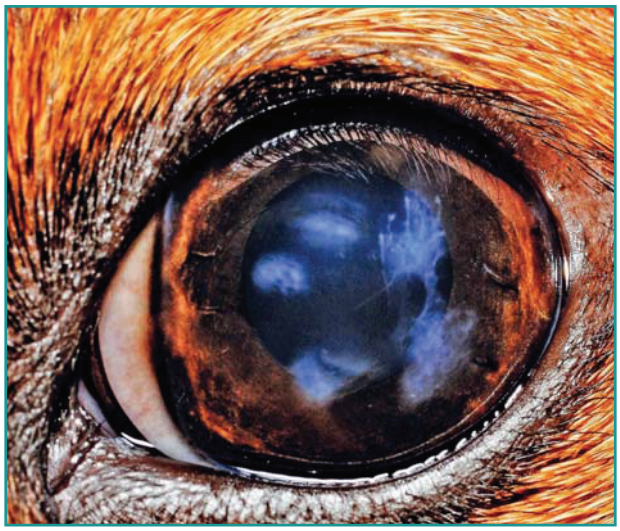

Figure 13 - PPM iris and multifocal endothelial fibroplasia in a dog (by biomicroscopy the lesion appears in the endotelium).

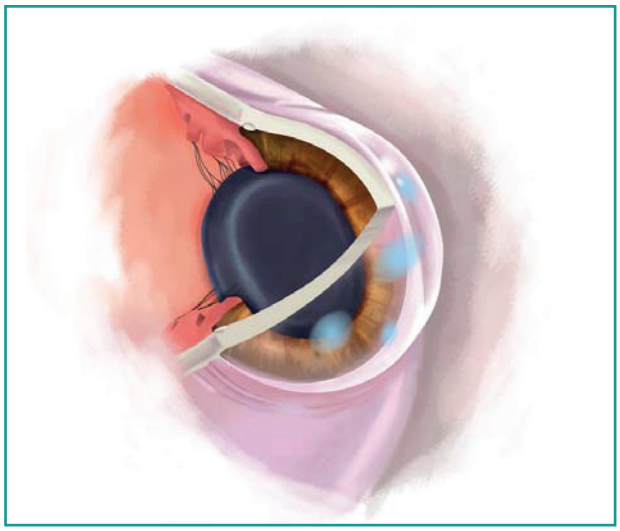

Figure 14 - Cartoon representation of endothelial fibroplasia.

retrocorneal remnant are substantial (visible with the naked eye) NO BREEDING. Minor (visible with 10x magnification only) retrocorneal remnants are drawn in the figures in the "drawing area" and are not ticked "undetermined" or "affected" for PPM.[34]

PREDISPOSED BREEDS

Transmission mode has not yet been established but it would not seem to be a simple recessive or dominant way. The predisposed breeds are Basenji but also Pembroke Welsh Corgi, Chow Chow and Mastiffs. The ECVO manual recommends to evaluate the PPM before dilation particularly in predisposed breeds: Basenji, Chow Chow, Petit Basset Griffon Vendeen and English Cocker Spaniel. PPM has also been reported in Miniature Bull terriers with ADAMTS 17 gene defects. However, it is unknown whether it is related to the altered gene or not.[20] Regarding the Italian breeds it is important to cite Bolognese and Italian Greyhound.[21] For cats instead the ECVO manual reports for risk of developing this pathology, the Bengal, the Burmese and the Persian.

Predisposed dog breeds are Basenji, Chow Chow, Petit Basset Griffon Vendeen and English Cocker Spaniel, Bolognese and Italian Greyhound, while for cats Bengal, Burmese and Persian.

COLLATERAL EXAMES AND DIFFERENTIAL DIAGNOSIS

PPMs can still be patent and this would lead to problems such as hyphema when you want to surgically intervene to the resolution. In human medicine, a percentage of 0.3% patent PPMs has been found.[10] Alario et al. have demonstrated circulation in a PPM of a cat thanks to a fluorescein angiography of the anterior segment of the eye.[22] Another sign that may indicate active circulation in PPMs is the visualization of saccular dilatations;[23] normally, thin PPM filaments are not vascularized while thicker ones are.[24]

Another complementary examination to implement before a surgical intervention that can clarify the involvement of the lens, is the ultrasound biomicroscopy (UBM). In cats, the most obvious differential diagnosis is the anterior synechia, which is frequently found in cats suffering from herpes post-partum. In fact, herpetic lesions complicated by infectious bacteria, can evolve into perforations with consequent phthisis bulbi or, in the luckiest kittens, in anterior synechia. The iris incarcerates in the injured area and indirectly allows the corneal healing process. Herpetic lesions occur in the post-natal period due to the transmission of herpes from the mother to the kittens as consequence of its reactivation following the stress of the peripartum. The diagnosis between synechia and PPM can be determined by looking at the tissue involved: pupil margin for synechia and iris collarette for PPM. In kittens the differential diagnosis between the two entities is sometimes difficult.

PPMs can be patent and thus have circulation inside. The main differential diagnosis is with synechiae.

MEDICAL AND SURGICAL THERAPIES

Therapeutic intervention is rarely necessary because iris-iris PPMs are not responsible for visual impairment. On the contrary, therapeutic intervention may be required if the DPMs are present and if the PPM forms a laminae. The possibility of seeing the fundus reflex with retro illumination may help in judgment.[25]. In human individuals, the «laminas» (caput medusae) are also responsible for amblyopia and exotropia.[26] The nystagmus has been described in veterinary medicine.[27] Therapy may be medical or surgical depending on the type of PPM or DPM. It is evident that in the case of iris-lens DPM, it is necessary to combine extracapsular surgery (phacoemulsification) to remove the cataract and refer to other texts for the surgical description.

- MEDICAL THERAPY

The only medical therapy, adaptable to veterinary medicine, for very extended PPM is the use of mydriatic agents (atropine, cyclopentolate and phenylephrine or tropicamide).[28] If there is insertion of PPM on the cornea with occurrence of edema, the use of hyperosmotic eye drops may be helpful.

- SURGICAL THERAPY

Surgical therapies described in the human literature include: iridoplasty/choreoplasty, Nd:YAG (neodymium-doped yttrium aluminum garnet) laser and combination of Nd:YAG argon laser.

1. IRIDOPLASTIC/CHOREOPLASTIC: a perilimbal incision is made at the top using a 2.4 mm keratome. Then viscoelastic is introduced in the anterior chamber and below the PPM to separate it from the iris and the anterior lens capsule. In case of tenacious adhesion, it could be necessary to move the PPM with a Sinskey hook or with the blunt cannula of the viscoelastic.[25] An excision is made with curved scissors (vannas) or with vitreous micro-scissors (in this case the corneal main port can be about 1.5 mm).[18,21] PPMs are then removed with forceps (Kelman-McPherson).

Therapy, when needed, includes medical therapy (midriatic drops) and surgical therapy. The latter can be divided into iridoplasty/coreoplasty and laser, such as Nd:YAG, or combination of Argon and Nd:YAG laser.

It may be helpful to use carbachol to induce myosis and assess if there are PPM residues accidentally not removed during surgery. The use of cortisone and mydriatics is recommended after surgery.[26]

2. USE OF YAG LASER: Vega and Sebates were the first to use Nd:YAG laser with good results in 1987[30] while Kumar et al. described complications, such as micro haemorrhages.[31] Although it is a flexible surgical technique, it can cause hyphema, dispersion of pigment in the anterior chamber, uveitis and cataract.[32] It may also lack efficacy in case of thick membranes.[25]
3. SEQUENTIAL SURGICAL USE OF ARGON LASER AND YAG LASER: the technique requires first the use of argon laser (100 µm spot size, 600 mw 0.1 s) on the junction area between PPM and iris collarette to narrow the vessels (coagulation effect). The second step requires the use of YAG laser (1 to 2 mj) for PPM rescission. The two steps should be performed on different days; the membrane remains attached to the anterior capsule of the lens but it retracts and reduces the visual deficit.[24,33]

ACKNOWLEDGMENT

I would like to thank Dr. Ilaria Iacobucci for assisting and helping with the translation to English.

- PPMs are a neurocristopathies due to defective regression of fetal vessels.
- According to the tissue PPMs have contact, they can show different clinical manifestations, such as corneal leukoma or cataract.
- No breeding for subjects with PPMs exception for PPM localized on the iris, PPM iris to iris or for pigment on the lens capsule or corneal endothelial fibrosis not visible with naked eye examination.
- Therapy is rarely required since PPMs are not normally responsible for blindness.

Membrane pupillari persistenti nel cane e nel gatto

Riassunto

Le membrane pupillari persistenti sono residui embrionali originati dalla neurocresta. Durante la vita embrionale, le membrane pupillari, hanno il compito di nutrire la lente in via di sviluppo ma perdono il loro significato nel momento in cui l'umore acqueo inizia ad essere prodotto. Infatti, poche settimane dopo la nascita si assiste alla loro atrofia; la persistenza ne rappresenta la caratteristica patologica. Le manifestazioni delle PPM sono varie: da residui iridei a filamenti fibrosi che prendono attacco sulla lente o sulla cornea (membrane pupillari displastiche). Nelle rare volte in cui è necessario fare terapia, si ricorre ad una terapia medica o rarissimamente chirurgica. Le razze principalmente predisposte alla patologia sono Basenji, Chow Chow, Petit Basset Griffon Vendeen, English Cocker Spaniel per i cani, mentre per i gatti ricordiamo il Bengala, il Sacro di Birmania e il Persiano. L'articolo ricorda i consigli d'allevamento nelle diverse manifestazioni cliniche.

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