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Ocular fundus abnormalities in cats affected by systemic hypertension: prevalence, characterization, and outcome of treatment

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Abstract

Objectives: To determine the prevalence of ocular fundus abnormalities in cats with a diagnosis of systemic hypertension, to characterize the abnormalities observed, and to evaluate ophthalmoscopic evolution during treatment with amlodipine besylate.

Animals studied: Cats diagnosed as affected by SHP in a two-year period.

Procedures: Systemic hypertension was assessed by oscillometric blood pressure measurement, and its etiology was also established. All the cats received an ophthalmic examination, and ocular lesions were classified with a score from 0 (no abnormalities) to 4 (severe abnormalities). All cats received amlodipine **besylate** by mouth, and those that showed fundus abnormalities were regularly rechecked from 7 to 365 days after diagnosis. Data were statistically analysed to compare P_{sys} and P_{dia} with all the variables and to correlate P_{sys} and P_{dia} with the fundus score.

Results: A total of 225 cats were enrolled in the study and the prevalence of fundus abnormalities was 58.6% (21.2%: grade 1; 18.2%: grade 2; 36.4%: grade 3; 24.2%: grade 4). Systemic hypertension was diagnosed concurrently with chronic renal failure (60.4%), hyperthyroidism (28.9%), both chronic renal failure and hyperthyroidism (7.6%), and hypertrophic myocardiopathy (3.1%). A significant effect of P_{sys} values on the fundus score was detected. Amlodipine therapy improved fundus abnormalities in 50% of cases at the 21-day follow up.

Conclusions: This study **showed** that fundus abnormalities are common in hypertensive cats at the time of the systemic diagnosis, and most of the abnormalities are moderate to severe. Treatment with amlodipine appeared to improve ophthalmic lesions over time.

Key Words: cat, eye, ocular fundus abnormalities, systemic hypertension, amlodipine

INTRODUCTION

Systemic hypertension (SHP) is defined as persistently high arterial blood pressure, and it is a recognized source of morbidity in both human and veterinary patients with specific systemic diseases.[1-13] Devastating damage caused by SHP is typically found in the eye, as well as the kidney, the heart and the brain.[4-5,8-9,11,13-25] Injury related to SHP in these organ systems is referred to as target organ damage (TOD), and is generally considered an indication for treatment with systemic antihypertensive drugs.

Systemic hypertension in cats is being diagnosed with increasing frequency perhaps because of the greater recognition of the disease and longer life span of cats.[1,7,13,30] Systemic hypertension is a common and complex syndrome in geriatric cats with a mean age of onset between 11 and 14 years.[1,7] Systemic hypertension can be essential (primary SHP) or secondary. Essential SHP, the most prevalent form of the disease in humans, is considered rare in cats.[1,31] Secondary SHP is associated with systemic diseases such as chronic renal failure (CRF), hyperthyroidism (HT), hyperaldosteronism, diabetes mellitus, and hypertrophic myocardiopathy (HCM).[1,5,12-13,19-20,23,31] The calcium channel blocker, amlodipine besylate, has been shown to be effective and safe in lowering systemic blood pressure in cats.[33]

In the feline eye, SHP can lead to sudden blindness caused by progressive microvascular choroidopathy and retinopathy up to the onset of optic neuropathy.[9,17,20,23,25,27] Hypertensive cats with ocular disease commonly present with subretinal or intraretinal hemorrhages, and partial or complete bullous retinal detachment.[9,20-21,23,25,27-28] Anterior segment abnormalities reported with SHP include hyphema and anterior uveitis. Hyphema may originate not only from anterior displacement of vitreal hemorrhages but also by iridal vessel damage from SHP. [1,20] Vitreous hemorrhages, in association with hyalitis, may also be present.[23,25] Ocular lesions secondary to SHP are usually diagnosed when a cat shows acute vision loss due to a complete retinal detachment. Less frequently ocular lesions due to SHP are observed during a complete examination of a cat diagnosed with SHP or as incidental findings during an ophthalmological evaluation.

Thus to date, the real prevalence of ocular fundus abnormalities in cats with SHP has not been well characterized. Although there are a number of studies on the effect of blood pressure on the animal eye, little information is available on the characterization of ocular fundus abnormalities and outcome after starting antihypertensive medical therapy.[9,20,21,23,25]

The aims of this prospective study were therefore to i) determine the prevalence of ocular fundus abnormalities in cats with a diagnosis of SHP; ii) characterize the abnormalities observed using a score from 0 (no abnormalities) to 4 (severe abnormalities); and iii) evaluate the ophthalmoscopic evolution during treatment with the antihypertensive drug, amlodipine besylate.

MATERIALS AND METHODS

This study was approved by the Agency for Animal Welfare of Pisa University and was developed with the collaboration of the Department of Veterinary Science (Pisa University), in cooperation with the Department of Animal Medicine, Productions and Health (Padua University and the San Marco Veterinary Clinic and Laboratory, Padua).

Two hundred and twenty-five cats with SHP were enrolled over a two-year period. All clinical data were catalogued using P.O.A.® System Plus v. 254.

Clinical examination

All cats underwent a complete physical examination that in our hospital routinely included measurements of the cardinal signs (body temperature, pulse, respiratory rate), hydration status, thoracic auscultation, abdominal palpation, and palpation of the ventral neck to detect enlarged thyroid gland. Systemic blood pressure was assessed using high-definition oscillometry (petMAP®, Ramsey Medical Inc, Tampa, Florida, United States).

Each cat was given 15 minutes to acclimatize to the clinic environment with the owner present, in a setting with no stimuli. Systemic blood pressure was measured before performing any clinical procedure. A cuff (width: 30-40% of circumference of the cuff site) was applied at the base of the

tail with the cat in a sternal-recumbent position. The same operator carried out three sequential measurements at one-minute intervals. Blood pressure values (systolic and diastolic) were calculated as the mathematical mean of the three measurements. The measurements taken in agitated or moving cats were eliminated, as were those in which the heart rate measured with the instrument differed from the heart rate measured manually by more than 50 beats per minute. Cats with a systolic pressure equal to or higher than 160 mmHg and diastolic pressure equal to or higher than 100 mmHg were considered hypertensive.

Blood and urine sampling

All the cats underwent diagnostic procedures, including laboratory diagnostics. All the blood samples were taken from the jugular vein. The urine samples were taken via cystocentesis. All tests were carried out at the same clinic (San Marco Veterinary Clinic and Laboratory) and always included: blood count with differential cells count, complete biochemical profile, coagulation profile, serum electrophoresis, thyroid function tests (TSH, TT4 fT4), and urine test (urinary dipstick, specific gravity on refractometer, osmolality, urinary protein to urinary creatine ratio, microscopic sediment).

Other tests

To formulate a reliable etiological diagnosis, each cat underwent a cardiology consultation (electrocardiogram and echocardiography) and, where necessary, imaging diagnostic procedures such as thoracic radiography, abdominal and thyroid ultrasound were performed.

Ophthalmic examination

Each cat underwent an ophthalmic examination, carried out in a visiting room where there were no stimuli, with minimal physical restraint. Complete ophthalmic examinations always included neuro-ophthalmic examination (palpebral reflex, assessment of menace response, pupillary light and dazzle reflexes), slit-lamp biomicroscopy (SL-15 portable Slit lamp, Kowa Company, Tokyo,

Japan) and indirect ophthalmoscopy (Heine Omega 500 Unplugged and Heine 30D lens; Heine Instruments, Herrsching, Germany). Retention of corneal sodium fluorescein dye (HS Haag-Streit International fluorescein, Switzerland) and intraocular pressure estimation (TonoPen Vet, Reichert Inc, Depew, NY, USA) were performed. Cats with anterior segment diseases (i.e. hyphema) that prevented complete ocular fundus visualization were excluded from the study. Clinical features and severity of fundus abnormalities secondary to SHP are summarized in Figure 1.

Cats with bilateral asymmetric fundus abnormalities were classified according to the grade of the most severe lesion. For the fundus photographic documentation, a digital fundus camera for veterinary use (Clearview, Optibrand LLc, Ft Collins, Columbia, United States) was employed. Vampire® (Vascular Assay and Measurement Platform for Images of the Retina) software modified for the feline fundus was used for image processing in 35 cats from the grade 0 group (no noticeable fundus abnormalities but clinically diagnosed with SHP).[26]

The calcium channel blocker amlodipine besylate was used as the primary therapy for all the cases (Amodip 1.25 mg, Ceva, Italy- 0.625-1.25 per cat once a day).

Follow-up

Cases were reexamined after diagnosis for up to one year. Follow-up visits were scheduled on days 7, 14, 21, 28, 45, 90, 180 and 365 from the beginning of the antihypertensive therapy (Figure 2). Cats whose owners failed to keep appointments were excluded from the study.

Data analysis

Categorical and continuous variables

Descriptive statistics were performed for the variables: sex (male/female), age group (<= 10 years, 10-12 years, 12-15 years, >15 years), breed, diagnosis (CRF, HT, both CRF and HT, HCM) and fundus score (from 0 to 4).

The central tendency was calculated for the systolic and diastolic blood pressure (P_{sys} and P_{dia}) variables and for the age groups. Tukey box-plot graphs were produced for the graphic visualisation of these distributions.

*Statistical analysis at T0 (time of **enrollment** in the study)*

After testing the normality of the data with the non-parametric Kolmogorov-Smirnov test, the Kruskall-Wallis test and Mann-Whitney test were used to compare P_{sys} and P_{dia} with all the variables. Spearman's rho was used to correlate P_{sys} and P_{dia} with the fundus score. The level of statistical importance was set for values of $P<0.05$.

Follow-up statistical analysis

To evaluate the therapeutic effect and clinical improvement, the following data were calculated:

1. the average time for improvement in fundus abnormalities according to the fundus score at T0;
2. the number of hypertensive cats with improved fundus abnormalities at each follow-up time;
3. the number of hypertensive cats with no ocular lesions from T0 to the last follow-up (day 365)
4. the number of hypertensive cats with minor improvements in fundus abnormalities;
5. the number of hypertensive cats with no improvement and/or deteriorated fundus abnormality

Software used

IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 22.0. Armonk, NY: IBM Corp.

Microsoft® Excel® 2011 Mac, v. 14.6.9

Dell™ Statistica™ 2015, v. 13.0

RESULTS

Descriptive statistics at T0 (time of enrolment in the study)

A total of 225 cats met the inclusion criteria, consisting of 133 neutered males and 92 spayed females. Thirteen breeds were represented: domestic short hair (n = 190), Persian (n = 16), Carthusian (n = 3), Siamese (n = 3), Bengala (n = 2), Norwegian Forest cats (n = 2), Ragdoll (n = 2), Sacred cats of Burma (n = 2), Abyssinian (n = 1), British short hair (n = 1), Exotic shorthair (n = 1), Maine Coon (n = 1), and Siberian (n = 1). The mean age at diagnosis was 12.5 years (range from 1 to 20 years with a median value of 12.5 years). The population was divided into four age **groups**: ≤ 10 years (n = 65; 28.9%), between 10 and 12 years (n =37; 16.4%), between 12 and 15 years (n = 67; 29.8%), and > 15 years (n = 56; 24.9%). Concurrent CRF, in addition to SHP, was identified in 136 cats (60.4%), 65 cats (28.9%) were affected by HT, 17 cats (7.6%) were affected by both diseases at the same time, and 7 cats (3.1%) were diagnosed with HCM.

The frequency of ocular fundus abnormalities previously classified in degrees according to the fundus score (from 0 to 4 as reported in Figure 1) was then calculated: 93 cats (41.4%) were classified as grade 0 (no abnormalities). Of the 35 cats in this group in which Vampire® was used, retinal imaging analysis showed a statistically significant reduction in the arteriolar mean diameter of 3.6 pixels (normal mean: 15.2 pixels) associated with an increase in the vein mean diameter of 25.22 pixels (normal mean: 6.2 pixels). Ocular fundus lesions were diagnosed in 132 cats (58.6%) and were categorized from grade 1 to 4 as follows: 28 cats (21.2%): grade 1; 24 cats (18.2%): grade 2; 48 cats (36.4%): grade 3; 32 cats (24.2%): grade 4.

P_{sys} and P_{dia} values (continuous variables) were correlated with the severity of fundus abnormalities (fundus score), which was more significant for P_{sys} than P_{dia} values (Fig. 3a).

P_{sys} and P_{dia} variables were then correlated to the diagnosis (Fig. 3b), to the age classes (Fig. 3c) and to the sex (Fig. 3d). Statistical analysis demonstrated no positive correlation between P_{sys} and P_{dia} and both diagnosis and sex. A positive correlation was found between P_{sys} values and age **groups**.

Lastly, P_{sys} and P_{dia} were compared with a dichotomic evaluation of the fundus (normal: no detection of fundus abnormalities; affected: detection of fundus abnormalities regardless of the severity). The results obtained showed a positive correlation and therefore a statistically positive effect of blood pressure values in determining fundus abnormalities (Fig. 4).

Follow-up evaluation

Of the 225 cats enrolled at T0, 14 died (n = 10 metabolic disease, n = 2 lung carcinoma, n = 1 mandibular sarcoma and n = 1 sepsis) with a median length of stay in the study of 45 days (range from 14 to 180 days). A complete follow-up evaluation (365 days) and ocular examination were then performed on 211 hypertensive cats.

At the first follow-up (7 days), most of the cats with a score greater than 0 (n = 132) showed changes in the ophthalmoscopic fundus evaluation, in particular: 1 cat (0.8%) worsened, and 117 cats (88.6%) improved at fundus examination. Fourteen cats (10.6%) showed no changes.

Fifty percent of cats showed a significant improvement of the fundic lesions 21 days post treatment commencement, with an average time of 36 days (Fig. 5).

At the last follow-up (365 days), 121/132 cats (91.6%) showed a significant improvement in the fundus appearance with retinal reattachment and resolution of the hemorrhages. However, different degrees of retinal degeneration were detected, as shown in Fig 6.

On the basis of the visual assessments, 71/132 cats showed an unequivocal visual function (normal menace response, normal dazzle reflex, normal pupillary light reflexes); visual function was judged uncertain in 31/132 cats (low menace response and dazzle and/or decreased pupillary light reflexes), while 30/132 animals were considered blind (menace response absent, dazzle and pupillary light reflexes inconsistent). Cats classified with grades 3 and 4 fundic lesions at the starting of treatment showed severely affected or absent visual function at 365 days follow up. In these cats severe or

diffuse secondary retinal degeneration was observed at indirect ophthalmoscopy, despite most of them showing retinal reattachment and/or resolution of the hemorrhages during the study period. Only one cat (domestic short hair, female, 10 years old) showed side effects due to amlodipine therapy. After six months of continuous therapy, oral proliferative lesions were observed and attributed to an adverse drug reaction (Fig. 7).

DISCUSSION

Ocular lesions are one of the most commonly detected complications in feline SHP. [1-13] In human medicine the first systematic approach to SHP and ocular lesions was by Keith, who proposed a four-grade classification of fundus lesions.[32] Although this classification remains the most widely cited grading system, several reviews have questioned its usefulness and relevance to current clinical practice.[33,34]A simplified grading system has been proposed in 2004 by Mitchell-Wong.[35] However, no consensus has been reached yet regarding the optimal method of classification for hypertensive retinopathy. To our knowledge, there are no published studies reporting a classification of fundus lesions associated with SHP in veterinary patients. In this study, we reported our grading system (from grade 0 to grade 4) based on human literature and developed on ophthalmoscopic features resulting from a previous preliminary study (unpublished data).

The aim of this prospective study was to classify and evaluate the prevalence and outcome of ocular fundus abnormalities in a population of hypertensive cats. The prevalence of ocular lesions in cats affected by SHP is difficult to establish because the most recent studies are all retrospective.[1,20,23,25] In the literature only one prospective study reports a 16% prevalence of ocular lesions in the examined population.[9] In our study 58% of cats showed fundus abnormalities in relation to SHP. Fundus evaluation is thus recommended as a non-invasive routine screening in cats with SHP. Previous studies identified a greater risk of developing ocular fundus lesions in females.[20,36] Our data differed from the literature, as 57.6% of cats with ocular lesions were males, and 42.4% were females.

The domestic short hair breed represented 84.4% of the entire population. Having assessed the low number of animals belonging to other breeds, it was not possible to statistically correlate the variable "breed" either with the prevalence of fundus lesions or with the values of systemic blood pressure. According to the literature, age represents a real risk factor.[9,20] In our study a statistically significant correlation was highlighted between the age **groups** and systemic blood pressure values. This is because older cats are at risk for underlying causes of SHP (i.e. CRF, HT). According to previous studies, and in the population we examined, CRF is the most common cause of hypertension.[20,23,33]

Lesions of the disc and the optic nerve have been described in cats with SHP but are difficult to diagnose clinically and thus can be considered more of a histopathological finding.[1] None of the cats enrolled in the study showed clear ophthalmoscopic signs of hypertensive optic neuropathy (i.e papilledema). In previous studies, animal patients were presented mainly on the basis of significant ocular signs (i.e. retinal hemorrhages, retinal detachment) secondary to SHP,[20,23] therefore these severe lesions were featured with greater frequency and/or more prominently. In the population we examined, 21.4% of the cats with ophthalmoscopic abnormalities showed mild lesions (grade 1). This reflects the importance of both a clinical and computer-assisted[26] fundus examination, even in hypertensive cats that do not show any visual impairment. **The results of colour fundus images processing using Vampire® algorithm in cats classified as grade 0 (no noticeable fundus abnormalities, but clinically diagnosed with SHP) demonstrated the potential role of the retinal image analysis in the early diagnosis of hypertensive retinopathy. The Vampire® algorithm used to measure vascular diameters and angles of arterial bifurcations contributed to the objective diagnosis of early damage to the ocular fundus as a result of SHP.[26]**

We also demonstrated a positive correlation between the severity of fundic lesions and the severity of blood pressure values. In fact, the severity of the lesions, expressed according to the proposed classification, correlated positively with blood pressure values.

It is generally reported that therapy with oral amlodipine improves the ophthalmoscopic lesions of the fundus; however, there is a lack of information in the literature regarding ophthalmoscopic and clinical improvements after the beginning of this therapy.[36-37] At the time of SHP diagnosis, all the cats in our study underwent oral amlodipine treatment and were clinically evaluated through scheduled follow-ups for up to 365 days. The population examined for the entire follow-up period included 211 cats. Fourteen cats died during the study with a median duration in the study of 45 days.

During the study period, 121/132 (91.6%) cats with a score greater than 0 showed a continuous and progressive improvement, 10 cats initially improved and then worsened, and only one cat continued to worsen despite the therapy. It was thus calculated that 50% of lesions improved in 21 days after the start of the therapy, with an average total time of 36 days.

Our results showed that amlodipine therapy is effective in reducing SHP damage to the fundus. In most cases it leads to retinal reattachment and hemorrhage reabsorption. However, at the last clinical evaluation (365 days after the diagnosis) only 71/132 cats had maintained their visual function, while 61/132 cats showed no or inconsistent visual function. These cats were also diagnosed with grades 3-4 of fundic abnormalities at first assessment, and showed severe retinal degeneration at the last clinical examination in the study period. The veterinary literature reports that long-term maintenance of vision is difficult to achieve in feline patients with ocular TOD due to SHP because of secondary retinal degeneration. The duration of retinal detachment is thus a critical factor: the shorter the period of detachment, the better the prognosis for the restoration and maintenance of visual function.[20,25-26] **A limit of our study is the impossibility to establish the real duration of retinal detachment. In fact many cats already presented different degrees of retinal detachment at our first clinical evaluation (T0).**

Oral amlodipine was considered a safe antihypertensive therapy; only one cat in this study showed oral proliferative lesions attributed to adverse drug reactions. Gingival hyperplasia is a well-known

side effect of amlodipine in humans, dogs and cats.[40,41] **Compared with other parts of the body** gingiva has the highest activity of transglutaminase, which is a calcium-dependent enzyme involved in apoptosis. Decreased intracellular calcium levels caused by amlodipine (calcium-channel blocker) reduces normal apoptosis and, hence, deregulation of tissue overgrowth contribut**es** to gingival enlargement[41]

CONCLUSIONS

Detecting subclinical hypertensive ocular fundus lesions enables treatment for SHP to be started before irreversible vision loss occurs. Early detection **includes** a fundus examination of all cats at risk of developing such lesions. Assessing **the prevalence of** hypertensive fundus lesions in cats is very difficult, as fundic assessment is usually performed in advanced stages of SHP and when vision has already been lost due to severe fundus lesions.

This prospective study demonstrated a high prevalence of ocular fundus lesions in cats with SHP (58%), and highlights the importance of subjecting all cats diagnosed with SHP to a complete ophthalmic evaluation. Our study also showed that cats with lower degrees of fundus abnormalities (grades 1-2) at SHP diagnosis **and receiving** amlodipine therapy have a better prognosis **for** maintaining visual function over time. **The average time to noticeable ophthalmoscopic improvement in cats receiving amlodipine was 36 days.** Many cats showing more severe fundus abnormalities at diagnosis, despite the improvement in fundus abnormalities with therapy, showed secondary retinal degeneration and poor or no visual function at the last clinical follow up.

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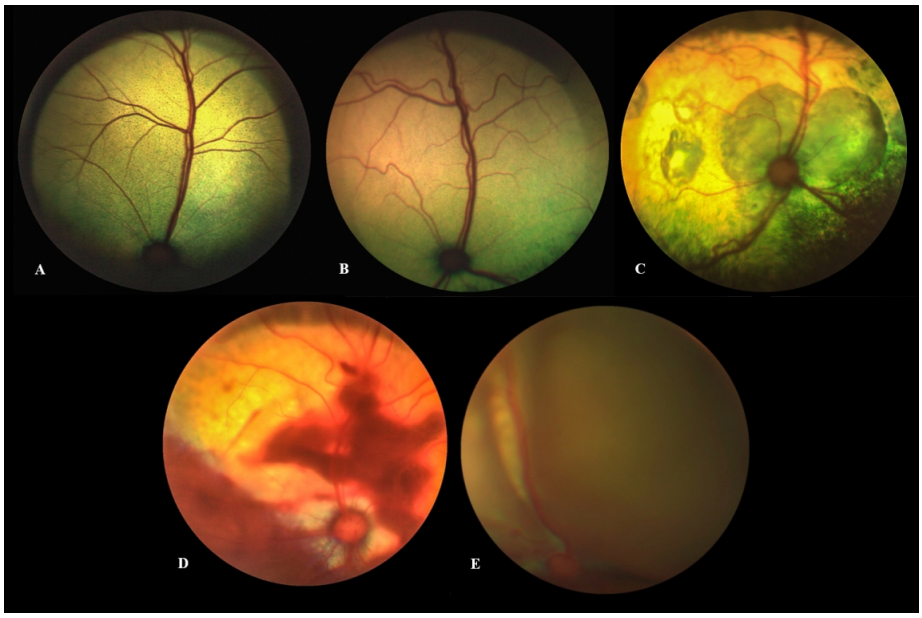

Fig. 1. Clinical grading of fundus lesions secondary to SHP. Grade 0: no noticeable fundus abnormalities, but clinically diagnosed with SHP (A); grade 1: increased arterial vascular tortuosity with minimal to moderate narrowing of the retinal arteries (B); grade 2: grade 1 abnormalities observed as well as mild retinal hemorrhages and/or subretinal exudation (bullous retinal detachment) (C); grade 3: grade 1 and 2 abnormalities observed with partial retinal detachment and moderate/severe retinal and/or vitreous haemorrhages (D); grade 4: grade 1 to 3 abnormalities observed as well as subtotal/total retinal detachment (E).

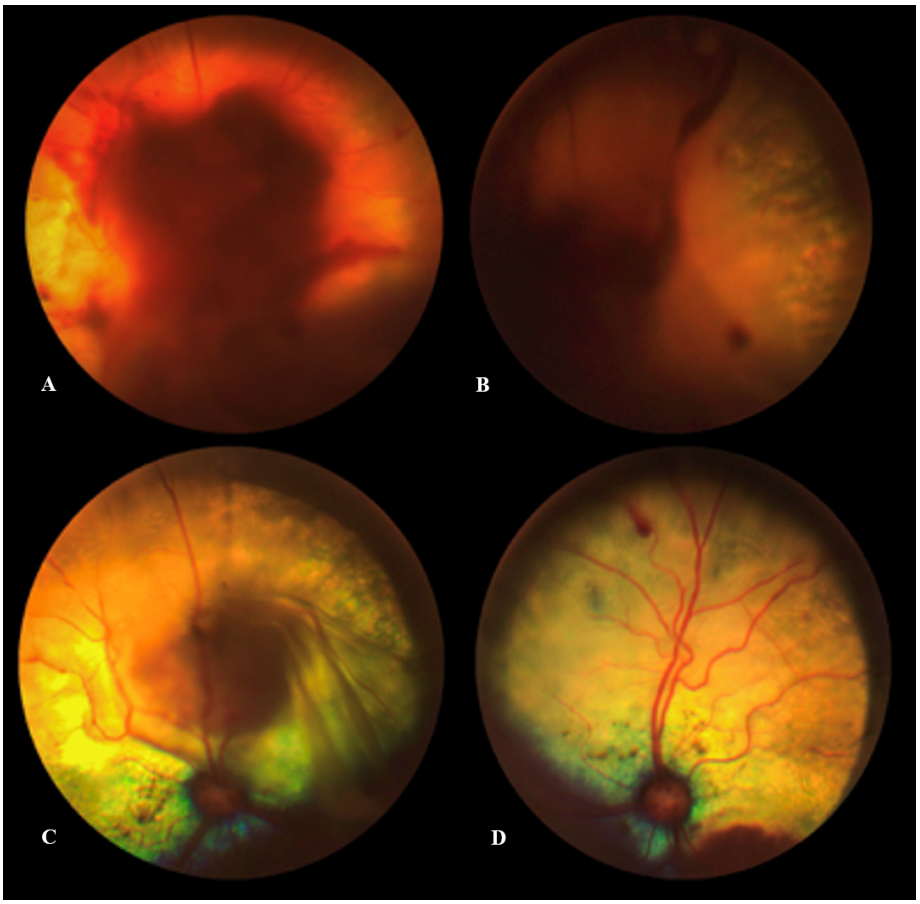

Fig. 2. Ophthalmoscopic follow-up in a cat with severe fundus lesions secondary to SHP (grade 4). Subtotal retinal detachment with pre-retinal, retinal and vitreous hemorrhages at the time of diagnosis (A). Improvement in the ophthalmoscopic aspects with retinal hemorrhage reabsorption 7 days after the beginning of amlodipine therapy (B). Fourteen-day follow-up shows improvement in the partial retinal detachment (C). Retina is almost completely reattached at the 21-day follow-up (D).

91x89mm (300 x 300 DPI)

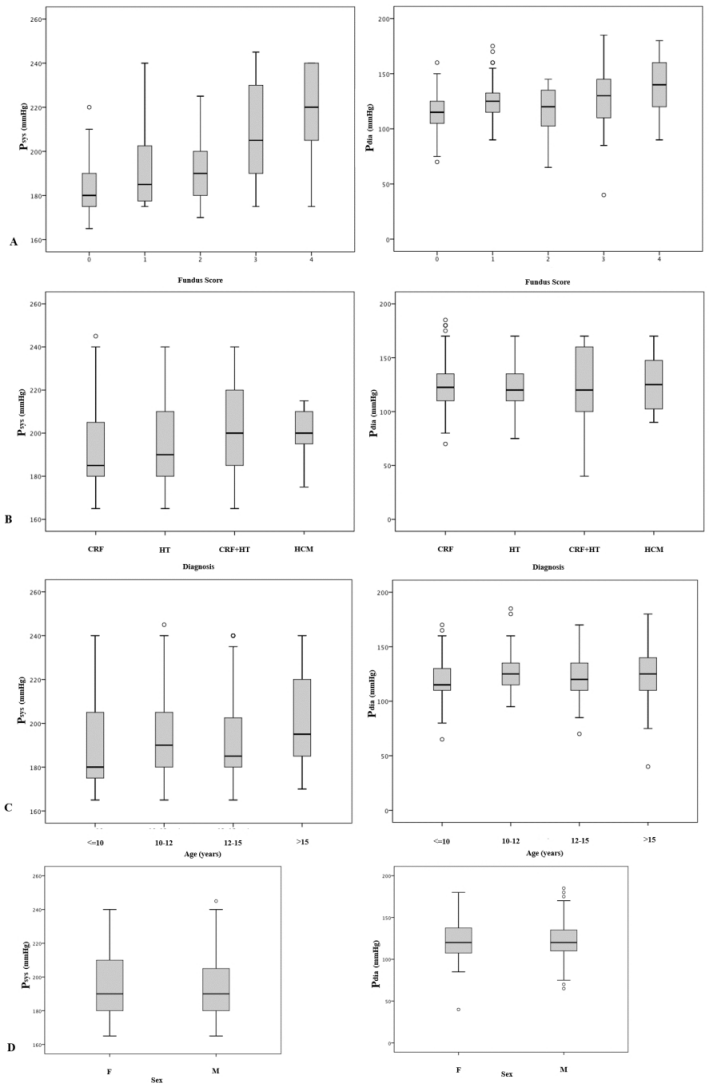

Fig. 3. Tukey box of the correlation between Psys and Pdia and the fundus score (A), with the diagnosis (CRF: chronic renal failure; HT: hyperthyroidism; HCM: hypertrophic cardiomyopathy) (B), with the age (C) and sex (D). All these comparisons were statistically significant with $P<0.05$.

137x201mm (300 x 300 DPI)

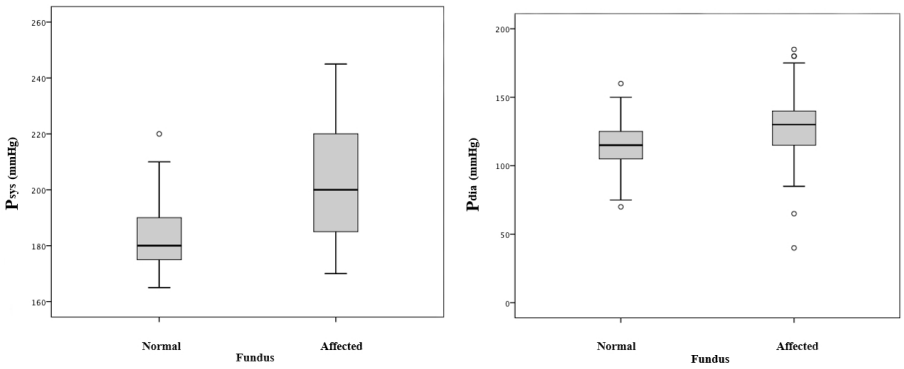

Fig. 4. Tukey box plot of the correlation between Psys and Pdia with a dichotomic evaluation of the fundus (normal, affected).

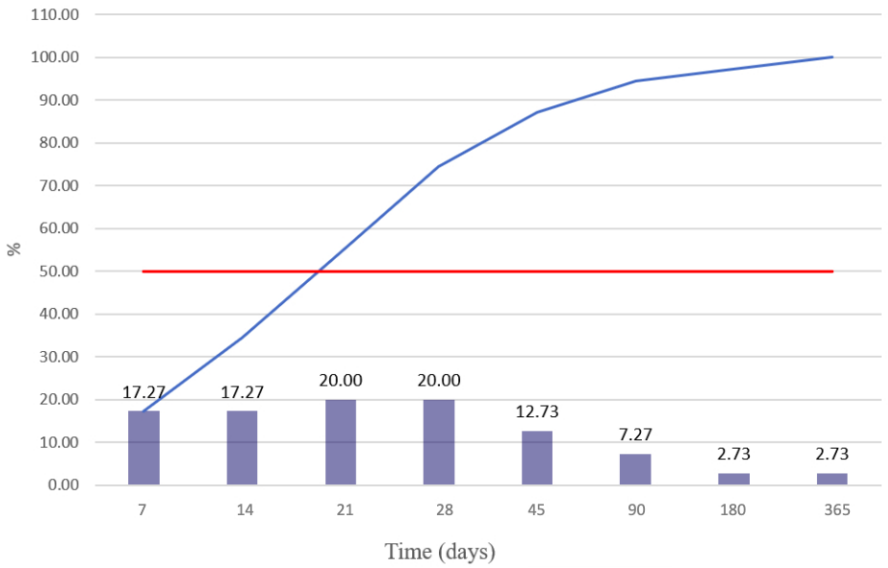

Fig. 5: Frequency of ophthalmoscopic improvement in fundus abnormalities at follow-up evaluations.

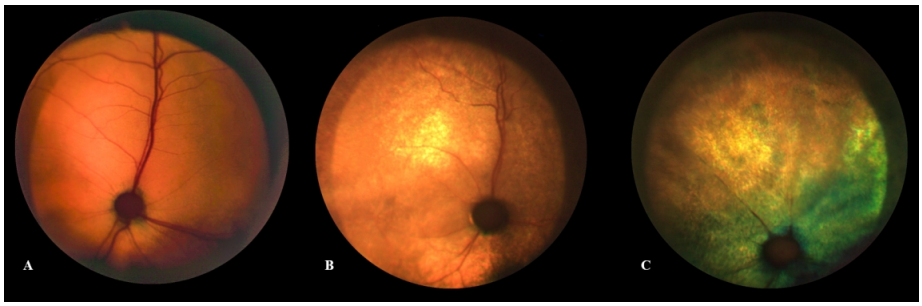

Fig. 6. Ophthalmoscopic follow-up in 3 different cases at 365 days after diagnosis. Complete retinal reattachment and reabsorption of retinal hemorrhages (A). Focal tapetal hyperreflectivity with initial vascular attenuation consistent with focal retinal atrophy (B). Diffuse vascular attenuation and tapetal hyperreflectivity suggestive of complete retinal atrophy (C).

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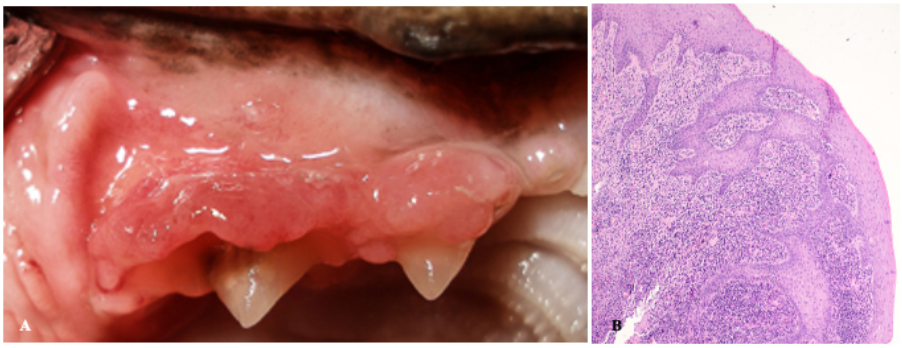

Fig. 7. Clinical features of amlodipine-induced gingival enlargement (A). Histological examination following gingivectomy showing hyperplastic multi-layered squamous epithelium, hematoxylin eosin staining, 4x (B).