Progressive Retinal Atrophy in the Abyssinian Cat

Clinical Characteristics

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Niney-four cases of a hereditary retinal degeneration in household Abyssinian cats were found in Sweden, mainly during a 3-year period. The disease was investigated by ophthalmoscopy, fluorescein angiography, electroretinography, and light microscopy. A bilateral retinopathy was usually first seen in affected cats at the age of 1.5-2 years. Fluorescein angiography did not demonstrate abnormalities of etiological significance to the disease process. A reduction mainly of a- and b-wave amplitudes in the ERG indicated a generalized photoreceptor disease. Light microscopy showed that the photoreceptor layer was primarily affected, while other retinal layers were mainly normal. The midperipheral and peripheral retina was affected more severely than the retina of the posterior pole until late stages of disease, when there was a generalized loss of photoreceptors. The clinical and laboratory findings suggest that PRA in these Abyssinian cats is a heritable photoreceptor degenerative disease with a fairly slow rate of progression. Invest Ophthalmol Vis Sci 26:193-200, 1985

Until recently, there were only a few reports on suspected hereditary retinal degenerations in the domestic cat. A generalized progressive retinal atrophy (PRA), possibly inherited, has been recognized in the Siamese1,2 and Persian3 cat breeds. In domestic mixed-breed cats an early onset photoreceptor degeneration has been reported4 that is dominantly inherited.*

PRA in the Abyssinian cat was recorded in Sweden in 1981.5,6 Seventeen parental matings were studied indicating that the disease was transmitted by a simple recessive gene.7 In the group of cats examined that were 2 years or older, 45% were affected. Cases of PRA in the Abyssinian cat also have been found in Holland (Stades F, personal communication, 1982), Finland,8 England,9 and Norway (Narfström K, unpublished observation).

In the present report, PRA in the Abyssinian cat will be described using animals examined as household pets, show, and breeding cats. For this reason, a detailed study of the early visual cell degenerative process was not performed. Studies now in progress, using known affected animals maintained in a controlled laboratory animal colony facility, will be reported in the future.

Materials and Methods

During a 3-year period, 94 cases of PRA in purebred Abyssinian cats were studied. Forty-two were male and 52 were female cats, the age varying from 7 months to 10 years. Sorrel and red Abyssinian coat colors were represented in approximately equal numbers. The cases were examined throughout Sweden, at cat shows, animal hospitals, and veterinary clinics using indirect ophthalmoscopy after dilatation of the pupils. None of the cats were laboratory animals; all were owned privately and kept as pets. Thirty-seven cats were available for reexamination a minimum of two times at a 6-month interval. Out of the reexamined cats, seven cases were followed at least four times in a 2-year period. In many cases retinal photographs were taken with a handheld fundus camera (KOWA RC2, Japan). In order to facilitate a description of the disease, the ophthalmoscopic lesions characteristic of PRA in the Abyssinian cat were divided into four stages according to severity: 1, 2, 3, and 4 (see Results). This was also for the purpose of simplifying a correlation of results of ophthalmoscopy and of other clinical investigations. In addition to the ocular examination, the general health status of each cat, including the food intake, was noted. Metabolic screening studies of plasma and urine amino acids

Fig. 1. Fundus photograph of a 6-month-old Abyssinian cat at a stage of suspected disease (stage 1). There is a gray discoloration (more obvious in color photographs) on both sides of the optic disk (arrows).

were performed in selected normal (four cats) and affected (six cats) Abyssinians cats (courtesy of Dr. P. Jezyk, University of Pennsylvania; Philadelphia, PA). Fluorescein angiography was performed in normal cats and in affected cats (8 months, 2, 4, 5, and 6 years of age) using a recycling motorized camera back and a strobe power unit that were connected to the handheld fundus camera. An excitation filter (Kodak Wratten gelatin Filter No. 47) and a barrier filter (Kodak Wratten gelatin filter no. 21) were utilized in conjunction with Ektachrome (200 ASA) color film. A 1.5-ml bolus of a 10% fluorescein dye solution was injected intravenously in the cephalic vein. Preinjection photographs were taken, followed by a series of 15–25 photographs during the first minute and then one to two photographs at 5, 10, 15, and 20 minutes postinjection.

Electrophysiologic investigations were performed in six normal cats and in seven affected Abyssinians at different stages of the disease process. The pupils were dilated using atropine and phenylephrine. The cats then were premedicated with atropine and xylazine (Rompun Vet; Bayer, Germany) and general anesthesia was induced and maintained with pentobarbital (3.5 mg/kg/hr) in Ringer’s solution, held under precise control through an infusion pump (Valley Lab, IV 5000b). During the procedure the cats were intubated, body temperature was regulated, and respiratory as well as pulse rates were monitored. Using a technique described previously in more detail, DC recordings of the electroretinogram (ERG) were studied. The technique included a suction contact lens (with a slightly opaque surface) applied to each eye and a reference chamber just behind the forehead, all of which were connected by saline-agar bridges to calomel half-cell electrodes. These were connected to low-drift DC amplifiers and a desk top computer system. Four responses were averaged. Dark adaptation time was 45 min. ERGs (a-, b-, and c-waves) were recorded in response to 1-sec white light stimuli from a xenon lamp reaching the contact lens via fiber optics. Stimulus intensities were varied in steps from slightly below the b-wave threshold to about 7 log relative units above the normal b-wave threshold. Amplitude studies for the a-, b-, and c-waves over the intensity range were performed.

Eyes for histopathology were obtained from eight cats with early (stage 2: three cats), moderately advanced (stage 3: three cats), and advanced (stage 4: two cats) PRA. The age of these cats varied from 2–6 years. For light microscopy the left eye from each cat was immersed in Zenker’s acetic acid or Bouin’s solution, rinsed with tap water, and stored in 70% ethanol. The eyes then were hemisected at the ora serrata, trimmed, and paraffin embedded. Sections were cut and stained with hematoxylin and eosin.

All investigations performed in this study were done in accordance with the ARVO Resolution on the Use of Animals in Research.

Results

Except for three cases of unrelated disease, the remaining 91 cats affected with PRA were in good physical condition. Most of them ate commercially canned cat foods or home-cooked diets that included fish and milk. The metabolic screening studies of plasma and urine amino acids failed to reveal any abnormalities (eg, plasma taurine and ornithine levels were normal). In none of the affected animals were cataracts present.

Ophthalmoscopy

Four main stages of retinopathy were established by ophthalmoscopy:

1. Stage of suspected disease (Fig. 1): A subtle gray parapapillary discoloration was seen on one or both sides of the optic disk, at times more marked in the region of the area centralis. No other abnormalities were present.
2. Early stage: The gray tapetal discoloration was more distinct and, in many cases, also present in the midperiphery of the upper temporal quadrant and always in the peripheral fundus. The peripheral vessels were, in most cases, slightly attenuated. The nontapetal fundus was normal.

3. Moderately advanced stage (Fig. 2): The tapetal discoloration was diffuse with dark and light gray areas, sometimes in conjunction with a mottled appearance. Hyperreflective parts of the fundus also could be seen, most often in the midperipheral and upper temporal tapetal fundus. The thinning of vessels was prominent, particularly in the periphery. In the nontapetal fundus discoloration was often seen, giving the area a mottled tan-gray appearance.

4. Advanced stage (Fig. 3): Generalized hyperreflectivity was seen in the tapetal fundus in older cats and the vessels were attenuated severely or not visible. In younger cats the hyperreflective changes were more prominent in the midperipheral and peripheral fundus while dark gray areas were often seen in the central retina mainly as streaks on both sides of the optic disk. Also in younger cats, some vessels near the disk were still patent but constricted. In both older and younger cats, severe degenerative changes were found in the nontapetal fundus as focal pale areas as well as heavily pigmented lesions in the form of streaks or clumps.

The retinal lesions described at stages 1–4 were always bilateral and at about the same stage of progression. There was no sex or coat color predominance among the affected cats.

The age distribution of the ophthalmoscopic lesions is illustrated in Figure 4. The PRA suspect category consisted of 10 animals. Most of these cats were 1–2 years old. In some, however, ophthalmoscopic findings suggestive of PRA were present as early as at 5–6 months of age (two cats) and later than 26 and 34 months (two cats). All animals having ophthalmoscopic lesions suggestive of PRA (stage 1) developed definite lesions (stage 2) within 2–6 months of the first examination. The progression of the disease was uniform in most animals. In general an early stage (stage 2) of PRA, found in a 1.5-year-old cat, had progressed to an advanced stage (stage 4) by 3.5–4 years of age. In some cases, however, the rate of progression varied.

Fluorescein Angiography

Fluorescein angiography was normal in a cat with an early stage (stage 2) of PRA (Fig. 5). In a moderately
advanced stage (stage 3) constriction of vessel diameter was seen, especially in the periphery. No other changes were evident in the angiograms at this stage. In the two advanced cases (stage 4), patent vessels could be observed in the central parts of the fundus; defects in the retinal vasculature were seen as attenuated vessel diameter. No definite intraretinal leakage was found. The angiogram in one of the advanced cases demonstrated slow choroidal filling in parts of the tapetal fundus as well as filling defects (Fig. 6). In the nontapetal fundus window defects were observed (Fig. 7), and there was an area with blocked fluorescence.

Electroretinography

Table 1 demonstrates the results of the amplitude studies at one of the high light intensities. The
amplitude of the b-wave was significantly decreased at all light intensities \( (P < 0.0005) \) in the PRA cases (stages 1, 2, and 3) compared with the controls, ie, already at the stage of suspected disease (stage 1), \( (P < 0.05) \). The degree of depression was related to the stage of disease (Fig. 8). The a-wave amplitude was also significantly lower at all light intensities for PRA affected cats (stages 1–3; \( P < 0.01 \)). For the c-wave, amplitudes were decreased mainly at the moderately advanced stage (stage 3) of disease. At the advanced stage of disease (stage 4), there were no recordable ERG responses.

Pathology

The early stage of disease (stage 2) showed rather limited degenerative changes in the photoreceptor cell layer, the peripheral parts of the fundus being more affected than the central ones. In the periphery, severely disorganized outer segments were found and the inner segments appeared shortened. The visual cell nuclei were reduced from seven to nine rows to three to five rows and some were pyknotic. Occasionally what appeared to be visual cell nuclei or possibly phagocytic cells were present in the ventricular space. In the midperipheral fundus the changes were similar, to those in the periphery or somewhat less pronounced (Fig. 9a). Centrally the photoreceptor outer segments were in places disorganized and reduced in length, in other places they appeared normal. Although some of the inner segments were shortened, most were normal. In this region the outer nuclear layer was reduced from nine to thirteen rows of nuclei to eight to nine rows (Fig. 9b). Apart from these changes in

Table 1. Dark adapted a-, b-, and c-wave amplitude values (mean and standard error of the mean) at one high light intensity of white light stimulus (5.17 log relative units above b-wave threshold) for normal cats and groups of cats at different stages of disease. Stimulus conditions identical for all recordings

<table>
<thead>
<tr>
<th>Group (no. of cats)</th>
<th>a-wave amplitude ( \mu V )</th>
<th>b-wave amplitude ( \mu V )</th>
<th>c-wave amplitude ( \mu V )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (6)</td>
<td>156 ± 29</td>
<td>1,127 ± 103</td>
<td>1,020 ± 122</td>
</tr>
<tr>
<td>Stage 1 (2)</td>
<td>53 ± 8</td>
<td>677 ± 66</td>
<td>825 ± 60</td>
</tr>
<tr>
<td>Stage 2 (2)</td>
<td>45 ± 11</td>
<td>520 ± 47</td>
<td>787 ± 20</td>
</tr>
<tr>
<td>Stage 3 (2)</td>
<td>20*</td>
<td>186 ± 16</td>
<td>205 ± 9</td>
</tr>
</tbody>
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* Only one cat had a recordable a-wave in the group.
four to eight rows. The outer plexiform layer was somewhat reduced in thickness, mainly in the peripheral and midperipheral retina. The other retinal cell layers appeared normal.

Severe degenerative changes of the outer retinal layers were seen in two animals with advanced stage of PRA (stage 4). In the younger cat, the peripheral fundus showed no or only a few remnants of inner segments. The outer nuclear layer was absent or was only one to three rows in thickness with many pyknotic nuclei. In the midperipheral fundus the degenerative changes were even more severe (Fig. 11a). Centrally (Fig. 11b) there were remnants of outer and inner segments. The outer nuclear layer was highly variable in thickness consisting of two to seven rows of nuclei. Also the outer plexiform layer was reduced in thickness and lacking in severely affected areas of the retina. In the older cat, the inner nuclear layer was often in direct contact with the photoreceptor layer, no other pathologic alterations were found in the retina at an early stage of PRA.

Moderately advanced stages of PRA (stage 3) showed a variety of retinal degenerative changes depending on the individual case and on retinal location. The peripheral and midperipheral retina again was affected more severely than the central parts and, in one case, parts of the midperipheral nontapetal retina were more severely affected (Fig. 10a) than the corresponding location of the tapetal retina. The retinal changes at this stage of disease consisted of extremely shortened inner segments, sparse remnants of outer segments, aberrant cells in the ventricular space (appearing to be photoreceptor nuclei or macrophages), and a reduction of outer nuclear layer nuclear number (in some areas only two to four rows were present while others showed four to six rows). Centrally the retina was better preserved. Both the outer and inner segments were consistently shortened and disoriented, however. In this region the outer nuclear layer was reduced to

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Fig. 9. Photomicrograph of a stage 2 case of PRA. In the midperipheral retina (a) the outer and inner segments are shortened and what appears to be a visual cell nucleus or a phagocyte (arrow) is seen in the area between the external limiting membrane and the pigment epithelium. The outer nuclear layer is reduced from eight to ten to three to five rows of nuclei. In the central parts of the retina (b) there is only minor disorganization of the inner and outer segments and a few appear shortened. The outer nuclear layer is reduced from nine to thirteen to five to seven rows (hematoxylin and eosin stain [H and E], X320).

Fig. 10. Photomicrograph of a stage-3 case of PRA. In the midperiphery of the nontapetal fundus (a) only remnants of the outer segments are seen and the inner segments are severely shortened. Pigment epithelial cells are enlarged and have pigmented processes that extend into the interphotoreceptor space. The outer nuclear layer is reduced to one to three rows and pyknosis (arrow) is seen. In the central parts of the tapetal retina (b) there is shortening of the inner and outer segments and the outer nuclear layer is reduced to four to five rows. Also, what appears to be a visual cell nucleus (arrow) is seen in the ventricular space. The outer plexiform layer is somewhat reduced in thickness (although less than in the midperiphery) (H and E, X320).
pigment epithelium (Figs. 12a, b). In some places a few sparse pyknotic photoreceptor nuclei and traces of an outer plexiform layer were discernible. The inner retinal layers and the pigment epithelium appeared normal. Furthermore, there were no alterations found in tapetal cells at any stage of the disease process.

Discussion

Although ophthalmoscopic findings at various stages of PRA were rather similar, the variation in age of onset of disease in a few cats was remarkable. Through the genealogy of the cats, it was found that certain families were affected early with a more rapid progression of disease, compared to other lines of cats that developed PRA at a later time. A possible explanation of this deviation may be genetic variation due to inbreeding.

Metabolic\textsuperscript{11} and nutritional\textsuperscript{12-14} factors must be considered in cats with retinal degeneration. Taurine deficiency retinopathy in cats, which has been studied extensively during recent years, causes initially a focal retinal lesion (feline central retinal degeneration)\textsuperscript{12} in the area centralis region as seen by ophthalmoscopy. Hyperornithinemia resulting from ornithine-\delta-aminotransferase deficiency was described in a cat with advanced retinal degeneration.\textsuperscript{11} The Abyssinian cats used in this study were in good health and received normal diets. No abnormalities were found in plasma and urine amino acids, thus ruling out systemic taurine deficiency and/or hyperornithinemia (causing gyrate atrophy) as potential causes of the retinal degeneration observed in the Abyssinian cats.

Fluorescein angiography revealed no alterations in the normal passage of dye at an early stage of disease. At a moderately advanced stage (stage 3), when the retinal changes were generalized, only minor abnormalities were observed in the angiograms. This suggests that the more severe fluorescein angiographic abnormalities were secondary to the retinal degenerative process.

There was a good correlation between the different stages of disease seen by ophthalmoscopy and the functional integrity of the retina demonstrated by ERG. Even though retinal alterations in early PRA (stage 2) were minor as seen by ophthalmoscopy and light microscopy the decreased a- and b-wave amplitudes confirmed a generalized photoreceptor disease.
Light microscopy at different stages of disease correlated rather well with ophthalmoscopic findings. The minor gray discoloration found in early cases seemed to represent mainly outer and inner segment alterations, such as shortening, disorientation, and possibly some accumulation of degenerative debris. The more marked color change and the minor hyperrefractive areas, seen in moderately advanced cases, corresponded to more severe degenerative changes at the outer and inner segment levels and in the outer nuclear layer. This resulted in a marked reduction in thickness of the entire photoreceptor cell layer. The widespread hyperreflectivity seen in advanced stages of PRA represented severe degeneration of outer retinal layers most often with the inner nuclear layer in direct contact with the pigment epithelium. The other layers of the cat fundus that may account for color and reflectivity changes, ie, the pigment epithelium and the tapetum, appeared normal as seen by light microscopy.

So far, generalized retinal atrophy in cats has been characterized only in one family of related mixed-breed cats as a heritable rod-cone dysplasia. The cats developed the disease extremely early, and an advanced stage of retinal degeneration was seen by 3.5 months of age. Also, abnormal electrophysiologic findings were seen early during postnatal differentiation. Histologically the disease was more pronounced in the posterior pole than in the periphery.

It is obvious that PRA in the Abyssinian cats of the present study is a specific photoreceptor disease, different from the photoreceptor dysplasia found in mixed-breed cats. The retina is in most cases ophthalmoscopically normal until animals are 1.5 years of age. Ophthalmoscopically visible retinal changes then appear, and the disease progresses to an advanced stage that usually is seen by the age of 4 years. In the ERG reduced amplitudes were seen in cats with early PRA as well as a successive decrease in amplitudes with progression of disease. Furthermore, in early cases of PRA the central retina is normal in some areas while degenerative changes are seen in the peripheral fundus. Similarly, the more advanced stages (stage 3 and 4) affect the midperiphery and the periphery more severely than the central regions. The clinical characteristics and the laboratory studies of PRA in these Abyssinian cats thus show a slowly progressive retinal degenerative disease. The working hypothesis is that the disease begins after retinal differentiation is completed. In support of this hypothesis is the ophthalmoscopically normal retina in young affected cats as well as areas of morphologically normal appearing photoreceptors in the posterior pole at an early stage of disease (confirmed in electron microscopy). In order to further characterize the pathophysiology of this retinal degenerative disease in the Abyssinian cat future studies will include detailed electrophysiologic and morphologic investigations, specifically developmental studies.

Key words: progressive retinal atrophy, retinal degeneration, ophthalmoscopy, fluorescein angiography, electroretinography, light microscopy, Abyssinian cat

References