Feline central retinal degeneration

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Seven domestic cats with feline central retinal degeneration (FCRD) were investigated by ophthalmoscopy, fluorescein angiography, electroretinography, and light and electron microscopy. Little or no increase in lesion size was observed ophthalmoscopically over periods as long as four years. Five cats showed normal rod electroretinographic (ERG) responses and abnormal cone responses. In one cat both rod and cone responses were abnormal and in one cat neither rod nor cone responses were abnormal. Electron microscopic studies of one cat with an abnormal cone ERG showed outer segment lamellar disorganization in cones outside of the focal lesion. In the FCRD-affected cat with no ERG abnormalities, ultrastructure of cones outside the focal lesion was normal. Fluorescein angiography did not demonstrate abnormalities of apparent etiologic significance.

Key words: feline central retinal degeneration, electroretinography, photoreceptor, cone degeneration, cone dysfunction, maculopathy, area centralis, fluorescein fundus angiography.

Retinal degenerations in the cat resulting from nutritional deficiencies or hereditary causes have been described. Feline retinal degenerations have also been observed wherein the etiology was not defined. Feline central retinal degeneration (FCRD) was described as a bilaterally symmetrical lesion of the area centralis sporadically encountered in the domestic feline population. The ophthalmoscopically visible abnormality was bilaterally symmetrical and ranged in size from a rounded lesion about the size of the optic disc to an ellipsoidal lesion as large as 10 disc diameters. The rounded lesion was characteristically limited to that portion of the area centralis temporal and slightly above the level of the disc, whereas the ellipsoidal lesion extended both nasally and temporally. Because it was postulated that FCRD could prove important to the study of maculopathies in man, and since the domestic cat is a widely used experimental animal in ophthalmic and vision research, we further define, in this report, this natu-
Table I

<table>
<thead>
<tr>
<th>Cat identity</th>
<th>Lesion type</th>
<th>Change in lesion size</th>
<th>Duration of observation</th>
<th>Electroretinography</th>
<th>Fluorescein angiography</th>
<th>Electron microscopy*</th>
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<tbody>
<tr>
<td>A</td>
<td>Small, focal</td>
<td>None</td>
<td>1 month</td>
<td>Normal rod, abnormal cone</td>
<td>—</td>
<td>Normal rods, abnormal cone o.o.</td>
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<tr>
<td>B</td>
<td>Band retinopathy</td>
<td>None</td>
<td>18 months</td>
<td>Abnormal rod, abnormal cone</td>
<td>Possible intra-retinal leakage</td>
<td>—</td>
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<tr>
<td>C</td>
<td>Small, focal</td>
<td>Slight enlargement</td>
<td>4 years</td>
<td>Normal rod, abnormal cone</td>
<td>intralesional hyperfluorescence</td>
<td>—</td>
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<tr>
<td>D</td>
<td>Large, elliptical</td>
<td>None</td>
<td>18 months</td>
<td>Normal rod, normal cone</td>
<td>intralesional hyperfluorescence</td>
<td>Normal rods, normal cones o.s.</td>
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<tr>
<td>E</td>
<td>Large, elliptical</td>
<td>None</td>
<td>12 months</td>
<td>Normal rod, abnormal cone</td>
<td>—</td>
<td>—</td>
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<tr>
<td>F</td>
<td>Small, focal</td>
<td>Slight enlargement</td>
<td>4 years</td>
<td>Normal rod, abnormal cone</td>
<td>intralesional hyperfluorescence</td>
<td>—</td>
</tr>
<tr>
<td>G</td>
<td>Large, elliptical</td>
<td>None</td>
<td>3½ years</td>
<td>Normal rod, abnormal cone</td>
<td>possible intra-retinal leakage</td>
<td>—</td>
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*In areas peripheral to central lesion.

rally occurring feline central retinal degeneration.

Materials and methods

Five female and two male adult FCRD-affected domestic cats of unknown age, acquired as a result of routine screening of animals available for research, form the basis for this study. Fourteen ophthalmoscopically normal adult domestic cats were utilized as normal control animals. All cats were housed and fed under routine animal colony conditions and were in apparent good health.

Cats were anesthetized for fundus fluorescein angiography with a 40 mg per kilogram intramuscular injection of ketamine HCl (Vetalar, Parke Davis & Co.). Two milliliters of a 10 per cent sodium fluorescein solution was injected via the cephalic vein and the photographic sequence was accomplished using a rapid recycling fundus camera (Fundus Flash II, Carl Zeiss) equipped with a Wratten 47A excitation filter and a Wratten 15 barrier filter.

For electroretinography, the cats were similarly anesthetized and, in some instances, supplemented by approximately 1 mg of succinylcholine HCl administered intravenously at 7-minute intervals. When the latter agent was used, the cats were intubated and ventilated. The technique for recording the electroretinogram (ERG) has been previously described.7,8

The ERG rod responses were recorded from all cats by stimulating the dark-adapting retina with red light flashes (intensity 3.3 log-foot-Lamberts before passing through a Wratten 26 filter) and with scotopically balanced stimuli which had previously been scotopically balanced in normal dark-adapted cats by matching long- (Wratten 26) and shortwave (Wratten 47, 47A, and 47B) stimuli. Scotopically balanced stimuli elicited equal ERG b-wave responses in normal dark-adapted cats. Rod responses were also isolated by stimulating the dark-adapted retina with flickering light stimuli of 5 and 12 Hz, frequency at 2.0 log-foot-Lamberts intensity.

Cone responses were isolated from the dark-adapted cat retina by flickering stimuli of 5, 12, and 30 Hz, frequency at 4.0 log-foot-Lamberts intensity. Previous studies in the cat have shown that cone responses can be isolated with high intensity stimuli presented at 30 Hz.9,10 We have also found that at frequencies greater than 3 Hz, flicker stimulation at high intensity suppresses the rod responses and isolates the cone responses. These cone flicker responses are identical to those recorded under the same stimulus conditions, but with sufficient background intensity (2.0 log-foot-Lamberts) to eliminate the rod contribution to the ERG.11

Immediately following the electroretinographic studies, three eyes from two FCRD-affected cats were removed and hemisected at the ora serrata. After removing the vitreous, the posterior eye cup was fixed in 2.5 per cent glutaraldehyde in 0.0845 M sodium cacodylate buffer (pH 7.4), and postfixed in 1 per cent OsO. The tissues were then dehydrated and processed for electron microscopy.12

Results

Bilaterally symmetrical round, elliptical, or band-shaped retinal lesions (Fig. 1) were present in the FCRD-affected cats (Table 1).
Fig. 1. A, fundus photograph of right eye of cat D showing ellipsoidal lesion temporal to disc and smaller satellite lesions (arrow) on nasal side of disc. B, fundus photograph of left eye of cat D illustrates the bilateral symmetry characteristic of FCRD. C, fundus photograph of right eye of cat C showing size of area centralis lesion in 1969. D, fundus photograph of right eye of cat C in 1974, showing increase in size of lesion during the four-year period. E, prefluorescein injection fundus photograph of left eye of cat B showing natural hyperfluorescence in temporal portion of band-shaped retinal lesion. Directing the light source nasally would cause that area to hyperfluoresce. F, fluorescein angiographic photograph of venous phase showing several pin-point leakages (open arrows) in the temporal and nasal portions of the band-shaped lesion of cat B.

In the two cats with the smallest size lesion, (cats C and F) some enlargement of the area centralis lesion occurred over a period of four years (Fig. 1, C and D). No progression in size of the ophthalmoscopically visible lesions was seen in the remaining cats.

Hyperfluorescence deep to the retinal vessels was present within all focal retinal lesions even prior to the injection of fluorescein (Fig. 1, E). Fluorescein angiography demonstrated possible intraretinal pin-point leakage in two of the more severely affected cats (Fig. 1, F).

With one exception, there was no difference between normal and FCRD-affected cats in regard to rod b-wave, amplitude, and latency characteristics when the dark-adapting retina received red light stimuli. In the one cat with a broad band-shaped area of retinal atrophy, a b-wave of smaller amplitude but normal implicit time was recorded.

Similarly, the rod response elicited from the dark-adapted retina with white and scotopically balanced stimuli (Fig. 2) as well as with scotopic flicker stimuli (Fig. 3) were identical to those recorded from the normal control animals. Again, only in the cat (B) with the broad band-shaped area of retinal atrophy was the rod b-wave amplitude decreased. In all cases, the implicit time was normal.

Fig. 3 also demonstrates the cone responses recorded from normal and FCRD-affected cats in response to high intensity
Fig. 2. Single-flash dark-adapted ERG’s recorded from a normal control cat and two FCRD-affected cats (A and B). Cat A had a small round-to-oval focal lesion involving only the center of the area centralis and cat B had a large band-shaped area of retinal atrophy affecting the area centralis and adjacent structures in the posterior pole. There were no differences in the ERG’s of the normal control and FCRD-affected cat A when white and scotopically balanced red and blue stimuli were presented to the dark-adapted retina. The amplitude of all the responses recorded from the FCRD-affected cat B were lower than for the normal control cats. Stimulus duration S; vertical calibration at lower right, 100 nV; horizontal calibration, 50 msec.

slowly flickering light stimuli (5 Hz.). In contrast to normal cats, all but one of the FCRD-affected cats showed a reduction in the cone b-wave amplitude and a slight prolongation in the implicit time. These findings were also seen at 12 and 30 Hz. frequencies, although the decrease in the cone b-wave amplitude was not as marked (Fig. 4). Reduction in the cone b-wave amplitude and an increase in the implicit time were greatest in the cat with the broad band-shaped area of retinal atrophy. In one cat (D) with a large ellipsoidal lesion having prominent nasal satellites, no cone flicker ERG abnormalities were detected (Fig. 4).

Light microscopic abnormalities of the focal retinal lesion were similar in all three eyes studied (Fig. 5). The center of the lesion area was characterized by a complete absence of photoreceptors and the outer nuclear layer. Away from the center of the lesion, there was a gradually increasing number of photoreceptor nuclei concomitant with the appearance of photoreceptor inner segments and outer segment fragments. Further away from the center of the lesion, the retinal photoreceptors assumed a normal appearance.

Electron microscopic examination of the focal lesion site in all three eyes showed identical abnormalities. The apical microvilli of the retinal pigment epithelial cells were closely apposed to the external limiting membrane and interdigitated with microvilli of the Müller cells (Fig. 6, A). The pigment epithelium was slightly thickened and appeared to contain more inclusions than normal for the cat. Large phagocytic granules were observed to contain a mixture of lipid, myelin-figures, granular, and cellular debris (Fig. 6, B).

In the cat (A) with the small round focal lesion located in the center of the area centralis, retinal fine structure peripheral to the focal lesion showed distinct cone outer segment abnormalities. These abnormalities consisted of disorganization of disc lamellae which were disoriented relative to each other (Fig. 7, A). An occasional cone outer segment showed only a bag of membranous vesicles (Fig. 7, B). The rod outer segments were normal.

In contrast, in the cat (D) with the large
Fig. 3. Fixed frequency (5 Hz.) rod (2.0 log-foot-Lamberts) and cone (4.0 log-foot-Lamberts) flicker ERG's recorded from a normal control cat and 2 FCRD-affected cats (C and B). Cat C had a small, round focal lesion involving only the center of the area centralis and cat B had a large band-shaped area of retinal atrophy affecting the area centralis and adjacent structures in the posterior pole. The rod flicker responses recorded from the normal cat and FCRD-affected cat C were the same. The amplitude of the rod flicker responses recorded from FCRD-affected cat B was markedly reduced. When compared to the normal cat, the cone flicker responses of both FCRD-affected cats were markedly decreased or absent. Vertical arrows indicate stimulus onset; vertical calibration at lower right, 100 μV; horizontal calibration, 100 msec.

Fig. 4. Cone flicker responses (stimulus intensity 4.0 log-foot-Lamberts) recorded at two frequency levels (12 and 30 Hz.) from a normal control cat and two FCRD-affected cats (B and D). Cat B had a large band-shaped area of retinal atrophy affecting the area centralis and adjacent structures in the posterior pole. Cat D had a large ellipsoidal lesion of the area centralis with prominent nasal satellite lesions. There were no differences in the cone flicker ERG recorded from the normal control cat and FCRD-affected cat D. The cone flicker ERG of cat B showed a marked diminution of the b-wave amplitude and a slight prolongation of the implicit time. Vertical arrows indicate stimulus onset; vertical calibration at lower right, 100 μV; horizontal calibration, 100 msec. for the left column, 50 msec. for the right column.

Fig. 5. Cone flicker responses (stimulus intensity 4.0 log-foot-Lamberts) recorded at two frequency levels (12 and 30 Hz.) from a normal control cat and two FCRD-affected cats (B and D). Cat B had a large band-shaped area of retinal atrophy affecting the area centralis and adjacent structures in the posterior pole. Cat D had a large ellipsoidal lesion of the area centralis with prominent nasal satellite lesions. There were no differences in the cone flicker ERG recorded from the normal control cat and FCRD-affected cat D. The cone flicker ERG of cat B showed a marked diminution of the b-wave amplitude and a slight prolongation of the implicit time. Vertical arrows indicate stimulus onset; vertical calibration at lower right, 100 μV; horizontal calibration, 100 msec. for the left column, 50 msec. for the right column.

Discussion

Cats affected with FCRD show bilaterally symmetrical ophthalmoscopically visible abnormalities ranging in size from focal lesions limited to the center of the area centralis to broad band-shaped lesions extending across the entire posterior pole of the fundus. Although some minimal enlargement of the lesion size was observed in two cats followed over four years, the lesions in the remaining cats were unchanged. Fluorescein angiography did not demonstrate vascular abnormalities that appeared significant to the pathogenesis of FCRD. Although hyperfluorescence was observed, this most likely was an accentua-
Feline central retinal degeneration

Fig. 5. Light micrograph of focal lesion and adjacent retina (R) from cat A. The photoreceptor cells are absent in the center of the lesion, but increase in number at the lesion edges. The tapetum (T) and choroid (C) appear normal. ×170.

tion of the normal tapetal fluorescence resulting from thinning of the overlying retina. This interpretation is supported by the normal pigment epithelial, choriocapillaris, and tapetal morphology seen by light and electron microscopy.

The ERG recorded from FCRD-affected cats with different ophthalmoscopically visible lesions showed that all but one cat had normal rod responses. The broad zone of retinal degeneration present in the one cat with an abnormal rod ERG was of sufficient size to account for the decreased rod b-wave amplitude. The presence of a normal rod b-wave implicit time in the ERG of this and all other FCRD-affected cats suggests that as far as the rod photoreceptor system is concerned, FCRD is a localized rather than a generalized disease process.

In contrast, the cone b-wave of all but one FCRD-affected cat was reduced in amplitude and the implicit time was prolonged in response to high-intensity intermittent light stimulation, an indication of a generalized cone abnormality. In one cat with a small focal lesion and an abnormal cone ERG, fine structural observation of retinal areas peripheral to the area centralis lesion showed that generalized cone outer segment abnormalities were present. In contrast, the cat with a large elliptical lesion of the area centralis but with no ERG rod or cone abnormalities had normal rods and cones outside of the lesion area.

FCRD has certain similarities to an experimental nutritional retinopathy produced in kittens wherein the early ophthalmoscopically visible lesions seemed indistinguishable from those observed in FCRD. Electroretinographic studies also demonstrated cone system abnormalities in those kittens similar to those seen in all but one of our FCRD-affected cats. However, the rod responses appeared involved early in the experimental retinopathy in that the rod b-wave, although normal in implicit time, was reduced in amplitude. With continued feeding of the experimental diet both the rod and cone responses rapidly deteriorated and generalized retinal degeneration was the end-stage.

Rabin, Hayes, and Berson suggested that FCRD and the dietary-induced retinal degeneration described by Morris were early and late stages, respectively, of their nutritionally induced retinopathy. There are, however, several significant differences between FCRD and their nutritional retinopathy. The most obvious difference was the rapid progression of the experimental disease. Whereas cats with FCRD showed no or minimal progression of the ophthalmoscopically visible lesion, kittens with the nutritional retinopathy rapidly progressed to complete retinal degeneration. Histologically, the retina in the nutritional retinopathy showed extensive and wide-
Fig. 6. Electron micrographs of lesion area. A, center of the lesion, cat A, right eye. The loss of photoreceptor cells is almost complete although three nuclei are present in this area, one of which is continuous with an inner segment (arrow). The apical villi (V) of the retinal pigment epithelium extend toward the external limiting membrane. A residual outer plexiform layer (OPL) is present adjacent to the inner nuclear layer (INL). x2,200. B, area adjacent to center of lesion, cat A, left eye. Photoreceptor cell nuclei are visible at the bottom of the picture. Residual inner segments and fragments of outer segments (arrows) occupy the space between the external limiting membrane and the pigment epithelium. The pigment epithelium contains a large phagocytic granule (G). The many electron-dense granules, presumably lipofuscin and lysosomal, in the pigment epithelium are normal in cat eyes although their number may be increased. The tapetum (T) and choriocapillaris (C) are normal. x3,000.
spread degeneration, a finding which has not been observed in FCRD. It also appears that the ophthalmoscopic appearance of the retina in their nutritional retinopathy can be correlated with the electrophysiological abnormalities. Kittens with "moderate-advanced stages" of retinopathy showed marked abnormalities in the rod and cone components of the ERG. In contrast, our three FCRD-affected cats with similar ophthalmoscopic lesions showed either a normal ERG (one cat) or only a decrease...
in amplitude and a prolongation of the implicit time of the cone b-wave (two cats).

To date, it would appear that FCRD may encompass two distinct entities. First, there is an ophthalmoscopically visible area centralis retinopathy (i.e., a maculopathy) with an associated generalized cone abnormality, a form that has interesting similarities to certain cone dysfunction syndromes observed in man.16-17 Second, in one FCRD-affected cat, an ophthalmoscopically visible area centralis retinopathy with no other retinal abnormality was demonstrated, a form that may correspond to maculopathy in man. These experimental models of retinopathy, if consistently reproducible, would provide a means of studying their pathogenesis and thus produce information potentially important to the understanding of similar retinopathies in man.

REFERENCES