An Electrophysiologic Approach for Early Diagnosis of Progressive Retinal Atrophy in the Norwegian Elkhound

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Disciplines
Eye Diseases | Medicine and Health Sciences | Ophthalmology | Veterinary Medicine

Comments
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Introduction

Progressive retinal atrophy is a common hereditary disease of dogs. Initially there is night blindness which progresses to complete loss of day vision, and results in complete blindness.

This disease was first investigated in Gordon setters in 1911 and was called "retinitis pigmentosa of dogs" because it clinically and histologically resembled retinitis pigmentosa in man. A report has described the disease in many other breeds. The heredity, developmental pathology and physiology of the disease in Irish setters was well described by Parry.

Recently, the ultrastructural pathology of advanced progressive retinal atrophy was described in the Norwegian elkhound, and the disease was termed photoreceptor abiotrophy because it was suspected that normal photoreceptor development preceded the degeneration.

The purpose of this paper is to summarize early aspects of the disease in the Norwegian elkhound and to briefly discuss an electrophysiologic approach to its early diagnosis.
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invasive and 1911 pigmentosa clinically and . A report has many other , developments in physiology setters was this report is based primarily on the electrophysiologic findings of these four litters, and the clinical findings in all 25 dogs.

Binocular indirect ophthalmoscopy was performed in all pups at monthly intervals until they were euthanized. A darkened room containing obstacles of varying size and shape was used for behavior testing. The animals roamed free in the room and their ability to avoid objects both in normal room light and in dim light was observed. Dogs eight weeks to five years of age were tested, although not all dogs were tested over the entire time period.

Material and Methods

Since October, 1968, 25 Norwegian elkounds and 20 control dogs have been examined at the Section of Ophthalmology, University of Pennsylvania School of Veterinary Medicine and the Wilmer Ophthalmological Institute, Johns Hopkins University School of Medicine.

In this group are included the results of test breedings. Two affected females were bred to a known progressive retinal atrophy-affected male. Four pups (2 males, 2 females) were produced in the two litters (litters A and B). The two affected females were then bred to a known-carrier male. Eleven pups (6 females, 5 males) constituted these two litters (litters C and D). This report is based primarily on the electrophysiologic findings of these four litters, and the clinical findings in all 25 dogs.

Electroretinography was performed according to a method previously described, but with some modifications. The dogs were treated with atropine sulfate administered intramuscularly, and their pupils were dilated with atropine sulfate (1% solution), phenylephrine (10% solution) and tropicamide (1% solution). The dogs were anesthetized with a short-acting thiobarbiturate, and in most instances, they were intubated, ventilated with a respirator pump and paralyzed with intravenously administered succinylcholine (20 mg/cc). In most animals six to ten mg succinylcholine was used.

A silver chloride electrode attached to a plastic scleral contact lens maintained contact with the cornea. Methylcellulose (1% solution) in saline served as a contact bridge. A stainless steel needle electrode placed subcutaneously over the masseter muscle served as the reference electrode, and the dogs were grounded by a subcutaneous needle electrode placed in the dorsal midline.
Electroretinographic responses were recorded on a standard four-channel paper recorder, using paper speeds of 100 mm/sec. and time constants of 0.3 and 1.0 seconds. In some tests, responses were amplified on a pre-amplifier (bandpass 0.8 Hz to 250 Hz) and displayed on a storage tube oscilloscope.

The electroretinogram (ERG) was elicited by stimulating with a 500 watt fan-cooled tungsten halide lamp (color temperature 3000 K) which was collimated with large condensing lenses and passed through heat filters and a beam splitter before being focused on a ¼ inch diameter fiber optic light guide.

The opposite end of the light guide was placed in the visual axis 1–2 mm from the corneal contact lens. A photographic shutter and rotating sector disc with equal dark/light ratio were in the path of the light.

A separate fan-cooled tungsten halide lamp whose beam was also passed through a heat filter, was also focused on the beam splitter. This light was used for maintaining the retina at a constant level of illumination.

The dogs were light adapted for three minutes at an intensity of 10 foot-lamberts.

After three minutes the background illumination was discontinued and the dogs were then dark adapted for 20 minutes. The flicker fusion frequency at different stimulus intensities was determined.

Animals were considered PRA affected if either (1) classical ophthalmoscopic findings were present in conjunction with blindness first at night and then total or (2) rod dysfunction was demonstrated to be absent by the methods used and was confirmed by either light or electronmicroscopy. Animals were considered non-PRA affected if normal rod and cone function could be demonstrated and neither ophthalmoscopic nor behavioral abnormalities were evident and no abnormalities were present when the eyes were examined microscopically.

Results

Both normal and affected young pups (eight—twelve weeks old) seemed to maneuver normally, avoiding collisions, through the obstacle course, both in room light and in darkness. Affected dogs six months old showed severe impairment of vision, being restricted to five feet.

There are a number of cases in which animals appeared to perform normally postoperatively, but did not appear normal clinically or electrophysiologically. Monitoring of these cases showed the photopic ERG was preserved or retinal function was retained for a time thereafter.

Results of PRA-Affected Case Arteriograms

Arteriograms revealed cases of arteriovenous anastomoses occurring in the posterior arterial arcade. This was confirmed by angiography and ultrasonic imaging, and these were not present in normal or non-tumorous dogs.

Visual acuity tests in these cases revealed that dogs with arteriovenous anastomoses had constriction of the area of the vascularized portion of the retina, as well as decreased and impaired visual acuity.

Cases were studied for all dogs, and while the photopic and dark adaptation responses were impaired, the retinal morphological and functional testing showed no abnormalities.
impairment of vision in dim light but normal vision in room light. By three to five years of age, affected dogs appeared blind both day and night.

There were no ophthalmoscopically detectable changes in affected animals before five months of age. After this the tapetal retina in the posterior pole showed a tan to brown discoloration with a swirling granular appearance. This change was most noticeable using diminished ophthalmoscopic illumination. These changes increased in intensity over six to eight months and were later replaced by tapetal hyperreflectivity, most marked in the posterior pole just above the optic nerve head. The superior tapetal retina one to two disc diameters away from the border of the tapetum retained the granular light brown discoloration until late in the disease. With time the entire retina appeared affected and was hyperreflective.

Retinal vascular thinning was not prominent until after two years of age. Arteriolar constriction appeared first with significant venular thinning occurring after the arteriolar caliber was greatly diminished. These changes were most prominent in the tapetal retina although they were present in the non-tapetal area.

Vascular changes were not restricted to the peripheral retina in early cases but appeared along the entire course of the vessels. In two dogs, arteriolar thinning seemed to be preceded by saccular dilatations and constrictions along the superocentral tapetal arterioles. The end result of the vascular changes was marked arteriolar and venular attenuation until the retina appeared avascular except for very small fine vessels in the optic disc and immediate peripapillary area. In the non-tapetal areas vascular shutdown appeared as the fine white lines of "ghost vessels."

Ophthalmoscopic changes in the non-tapetal retina were not as marked and were not seen until the later stages of the disease. Most consistently the dark brown color produced by pigment in the pigment cell layer became mottled, pale areas appearing interspersed with dark brown zones. In two dogs, 3.2 and 4.5 years old, ophthalmoscopy failed to reveal abnormalities despite behavioral and electrophysiological findings compatible with the presence of the disease.

Dark adapted flicker electroretinography was first performed at six weeks of age in litters C and D and at 10 weeks of age in litters A and B. In litters A and B (affected x affected cross) 3 dogs had no scotopic (rod) function at 10 weeks of age. Another died of aspiration pneumonia prior to
establishment of diagnosis. In litters C and D (affected x carrier cross) three of eleven dogs were diagnosed as affected by the initial absence of rod function. Repeat examination of the remaining eight pups failed to demonstrate electrophysiologic or ophthalmoscopic abnormalities.

Age matched normal and affected dogs responded similarly to high intensity rapidly flickering light similarly. Affected dogs did not respond to the low intensity slowly flickering light. In affected pups, the flicker threshold was consistently elevated, and no response was recordable when stimulating with low intensity, slowly flickering light. This abnormality was detected at six weeks of age in dogs tested that young and did not change in several examinations as the dogs grew.

Discussion

One of the diagnostic features of progressive retinal atrophy in the dog has been an absence of ERG response to single flash stimuli in the dark adapted state. Similarly in retinitis pigmentosa of man, which is similar in behavior to progressive retinal atrophy, the ERG is extinguished. Because of this, electroretinography is used to differentiate retinitis pigmentosa from the ophthalmoscopically similar pseudoretinitis pigmentosa.

Some contend that the ERG is present, although of extremely low magnitude, and failure to record the response may be due to inadequate stimulus or inability to recognize the response in the ambient “noise” of the recording system. In the latter case computer averaging techniques have demonstrated an ERG to be present in some patients in the advanced stages of retinitis pigmentosa.

Using very high stimulus intensities, photopic flicker responses were obtainable from patients with retinitis pigmentosa. These responses became extinguished using only single flash stimuli. More recently normal photopic responses were recorded while rod activity was absent in young patients with retinitis pigmentosa.

Flicker fusion electroretinography has been shown to be a method by which rod and cone function can be separated. The canine ERG has been recorded after stimulation with intermittent stimuli of varying intensity. Fusion, the inability to record individual responses to repetitive stimuli, in
the dog occurred slightly above 7 to 10 Hz under scotopic conditions, while photopic (cone) fusion, using higher stimulus intensities, was found at 60 Hz. As in other species, the resulting curve, obtained by varying light intensity and frequency, is bipartite, separable into initial scotopic and later photopic components.

We were able to reproduce the bipartite fusion frequency curve in the dog. The scotopic fusion values we obtained in normal dogs were consistently higher (20 Hz) than those previously reported, which may be attributable to differences in recording equipment or stimulus intensity, or both.\textsuperscript{12}

Studies in which small areas of retina were stimulated amply, demonstrated that scotopic and photopic function were separable and that only photopic functions were recordable from pure cone areas (ie - the rod-free fovea) and only scotopic function could be elicited from the relatively cone free retinal periphery. In areas in which both cell types were present, the typical bipartite curve was recordable.\textsuperscript{7}

The absence of responses to low intensity slowly flickering light as early as six weeks (and consistently thereafter) in affected animals indicates that scotopic or rod activity is defective at an extremely early age, contrary to classical clinical descriptions which claim that the cells develop and function normally prior to degeneration.\textsuperscript{15,9} The absence of rod-mediated activity, which is found consistently from six weeks of age onward, is verifiable by extensive rod receptor abnormality seen electronmicroscopically. The subsequent loss of response to higher intensity rapid frequency stimulation indicates the progressive nature of the disease, as the cones become affected. This was confirmed electronmicroscopically also.

In summary, we have shown that by ophthalmoscopic examination and a definitive diagnosis of progressive retinal atrophy cannot be made before one year of age. The classical ophthalmoscopic findings of tapetal reflectivity and vascular thinning are usually not present until about two years of age. Behavior testing, at best, is highly unreliable.

By electroretinography the disease can be diagnosed at six weeks of age, and probably earlier if necessary. The absence of recordable rod activity is verified by the extensive rod receptor pathology seen electronmicroscopically.
References


