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Maculas, monkeys, models, AMD and aging

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Abstract

Age related macular degeneration (AMD) signs may be found reliably in monkeys (Macaca mulatta) bred selectively in Florida after 14 generations of inbreeding in a closed colony at the University of Puerto Rico. Progression, ultrastructure and functional losses are parallel to those found in humans.

Keywords: ARMD; Macula; Monkeys; Drusen; Models; Surrogate

1. Introduction

The word "model" is defined by Webster's unabridged dictionary (McKechnie, 1968), as (primary definition) "anything of particular form, shape, size, quality, construction intended for *imitation*"; a form in miniature, in natural size or something made of similar proportions (or) (secondary definition) as "an imitation or copy in *miniature* of something already made or existing on a large scale..."

Twenty years ago, we began asking questions about an AMD (age related macular degeneration) model in inbred non-human primates (NHP) (e.g. Dawson, Ulshafer, Engel, Hope, & ad Kessler, 1989; Hope et al., 1992). In 1984–1988, we had the opportunity to examine a large number of eyes in the closed rhesus macaque (*Macaca mulatta*) colony that has populated, since 1938, a small island off the east coast of Puerto Rico, Cayo Santiago. The Cayo Santiago macaques are the oldest continuous monkey colony in the hemisphere and are well known in the fields of social anthropology and primatology (Rawlins & Kessler, 1986). The eye studies have disclosed a surprising frequency of varied clinical signs typical of human glaucoma and AMD (e.g. Anderson, Dawson, Gonzalez-Martinez, & Curcio, 2006; Dawson et al., 1989; Hope et al., 1992).

To maximize AMD expression, a small selective-breeding colony was established at the University of Florida in 1994. More intense longitudinal study during 1995–2007 has allowed the documentation of the NHP progression of the same major variables which are used in the human clinic for the diagnosis of AMD and its staging (Abdelsalam, Del Priore, & Zarbin, 1999). The majority of the clinical signs are obtained by fundus examination, fundus photography or fluorescein angiography. Previously, for NHP, these have never been assembled in one publication. Here, we assemble the typical clinical evidence and sample related data on history and function in order to provide the most complete overview of this emerging resource.

2. Methods

As in the clinic, the major data source has been fundus appearance. The fundus camera is a table mounted Zeiss type F which was modified to accept a Canon EOS type digital camera back. In order to eliminate artifacts and eye movements the animals were sedated by 10 mg/kg ketamine, a tracheal catheter placed, and paralyzed with intravenous (3.2 mg/kg) pancuronium bromide. Subsequently, ventilation was assisted and expired gases were analyzed for end-tidal CO_2 and adjusted to approximately 40 mmHg. Pupils were dilated by 2% phenylepherin drops and tropicamide and corneas were fitted with hard corrective contact lenses. During assisted breathing, the gas mixture was 30% oxygen and 70%

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nitrous oxide. The respiration pattern and reflex movements were used as an indicator of recovery from paralysis. On recovery, neostigmine (5 mg/kg) was provided subcutaneously for the elimination of residual pancuronium. Procedures were approved by the University of Florida Institutional Animal Care and Use Committee.

Following 25° fundus image recording with emphasis on the macular region, fluorescein angiograms were recorded bilaterally. In order to obtain early and later-phase angiograms a 10% sodium fluorescein bolus in 3 ml saline, was injected into the femoral vein and an image was acquired every 2 s for 30 s. After a 3 min delay, late-phase images were acquired in order to examine possible leakage. Fundus image and fluorescein angiogram data have been acquired every 6 months, from all animals in the University of Florida aging monkey breeding program since initiation in 1995. A sample of the diversity of the fundus imagery is provided as a descriptor of the clinical fundus conditions. Non-periodic, related data on histopathology and receptor recovery-function is in the discussion.

3. Results

Figs. 1–6 cover the range of abnormal fundus signs we see in the Cayo Santiago derived Florida rhesus. Fig. 1 is a 25° field, normal fundus image from a female rhesus monkey, middle aged adult at 12 years of age. A very well demarcated circular parafoveal reflex is shown. It has a centralized golden hue probably of macular pigment origin. The optic nerve head disc shows small-vessel indications of minimal cupping. The temporal border of the disc is sharp with a well defined pigmentary rim coat. Overall, pigment is smoothly distributed and blood vessels of the arcade are not tortuous.

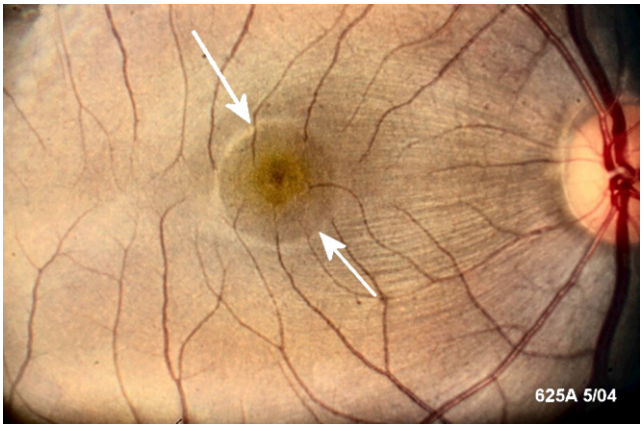

Fig. 1. Fundus image of a normal rhesus adult eye. Arrows mark the parafoveal reflex.

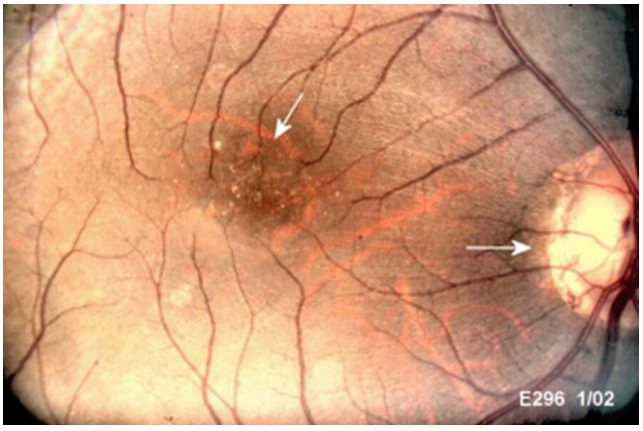

Fig. 2. Older adult fundus with macular hard, confluent and soft drusen. Arrows mark peripapillary retinal atrophy and disorganized macular pigmentation.

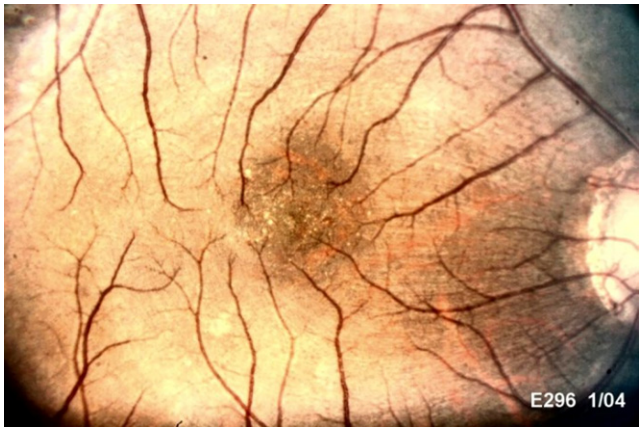

Fig. 3. Fundus of eye from Fig. 2 after 2 years of progression.

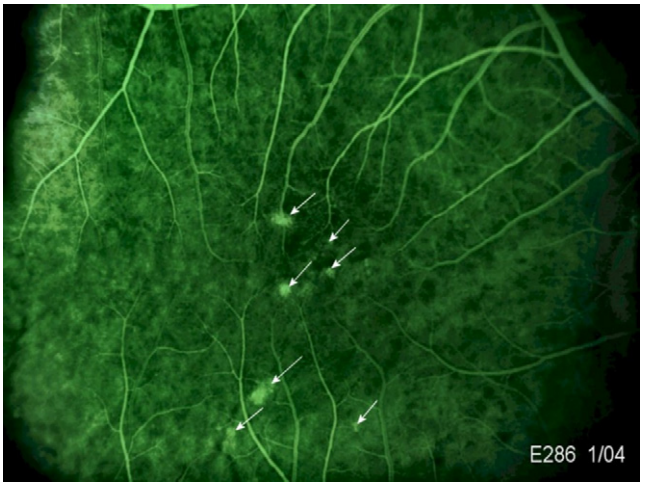

Fig. 4. Fluorescein angiogram in the early venous phase. Arrows mark window defects that locally uncover the choriocapillaris.

Fig. 2 is from a representative older adult animal, E296, 23 years of age. Particularly noticeable is the lack of definition of the parafoveal reflex and the unevenly pigmented central areas. There are marked peripapillary dystrophic changes of the retina immediately temporal to the optic nerve disc. The disc appears significantly more cupped than in Fig. 1. In the parafoveal region appear small and large, sharply defined cream-colored[1] drusen which in the more central areas appear to be in the process of coalescencing.

[1] For interpretation of the references to color in the text, the reader is referred to the web version of this article.