Purpose: To investigate the Insulin-like growth factor-1(IGF-1R) receptor expression on OFs, observe the inflammatory responses in the model, explore the important role of B cells in TAO.

Methods: Orbital fibroblasts obtained from 15 patients with TAO and from 15 control subjects were used to set up primary cultures, and were identified by immunohistochemistry. B lymphocytes were isolated from peripheral blood obtained from 10 patients with TAO and 10 controls. B cells were enriched, purified using immunomagnetic beads separation techniques and analyzed by flow cytometry.

3. The depleting effects of Rituximab on B cells at several concentrations in different time were measured by MTS. The inhibition on the expression of IL-6 and RANTES after using RTX and IGF-1 binding protein on the co-culture model were analyzed by ELISA.

Results: 1. The co-culture of orbital fibroblasts and B lymphocytes was established.

2. The expression of IGF-1R on OFs in patients with TAO was significantly higher than normal’s.

3. The expression of IL-6 and RANTES in each co-culture group was increased at 24 hours, especially in the T+T group (B lymphocytes and orbital fibroblasts all obtained from the TAO patients) is the highest.

Conclusions: An in vitro model that partially represents TAO, as an autoimmune inflammatory disease, was established by co-culture of orbital fibroblasts and peripheral B lymphocytes. The interactions between the two cells may play a role in TAO pathogenesis. IGF-1R may be the pathway in the interactions between OFs and B cells. It may mediate the process of TAO. Inflammatory responses may be depressed after blocking the receptor. B cell depleting agents RTX have a good anti-inflammatory effects in the vitro model. Monoclonal anti-CD20 antibody therapy may be a novel treatment option in TAO in the future.

Commercial Relationships: Renyan Wang, None

Program Number: 1844 Poster Board Number: A0040
Presentation Time: 11:00 AM–12:45 PM

Catestatin-like immunoreactivity in the rat eye

Maren Kriechbaum1, Oliver W. Gramlich1, Katrin Lorenz1, Franz H. Grus2, Daniela Ehrlich2, Christian Humpel2, Reiner Fischer Colbrie1, Nikolaos E. Bechrakis3, Josef Troger4
1Experimental Ophthalmology, University Medical Center Mainz, Mainz, Germany; 2Department of Psychiatry and Psychotherapy, Laboratory of Psychiatry and Experimental Alzheimers Research, 6020 Innsbruck, Austria; 3Department of Ophthalmology, Medical University of Innsbruck, 6020 Innsbruck, Austria; 4Department of Ophthalmology, Medical University of Innsbruck, 6020 Innsbruck, Austria.

Purpose: The aim of the study was to investigate the presence and distribution of the chromogranin A-derived peptide catestatin in the rat eye and trigeminal ganglion.

Methods: Western blots were performed in an attempt to characterize the immunoreactivities detected by the catestatin antiserum and the distribution pattern was explored by immunofluorescence.

Results: Sparse immunoreactive nerve fibers were visualized in the corneal stroma, in the chamber angle, in the sphincter muscle but also in association with the dilator muscle, in the stroma of the ciliary body and processes, but dense in the irideal stroma, around blood vessels at the limbus and in the choroid and in cells of the innermost retina representing amacrine cells as identified by colocalization with substance P. Furthermore, catestatin-immunoreactivity was detected in the trigeminal ganglion in small to medium-sized cells and there were abundant catestatin-positive nerve fibers stained throughout the stroma of the ganglion. Double immunofluorescence of catestatin with substance P revealed colocalization both in cells of the trigeminal ganglion as well as in nerve fibers in the choroid. The immunoreactivities are present obviously as free catestatin and/or small-sized catestatin-containing fragments in the retina and ocular nerves but as large processed fragments as well, weak in the retina and more prominent in remaining ocular tissues, possibly in endothelial cells.

Conclusions: The results indicate that this peptide is a constituent of sensory neurons innervating the rat eye and the presence in amacrine cells in the retina is typical for neuropeptides. Catestatin is biologically highly active and might be of significance in the pathophysiology of the eye.

Commercial Relationships: Maren Kriechbaum, None; Oliver W. Gramlich, None; Katrin Lorenz, None; Franz H. Grus, None; Daniela Ehrlich, None; Christian Humpel, None; Reiner Fischer Colbrie, None; Nikolaos E. Bechrakis, None; Josef Troger, None

Program Number: 1845 Poster Board Number: A0401
Presentation Time: 11:00 AM–12:45 PM

Spheroidal degeneration in H626R TGFBI corneal stromal dystrophy: clinical, genetic, histopathologic, immunohistochemical, and ultrastructural analysis

Kevin Lai1, Jason Reidy1, Benjamin Birt2, Tatiana Milman1
1Ophthalmology, New York Eye and Ear Infirmary, New York, NY; 2Ophthalmology, University of California, San Francisco, San Francisco, CA.

Purpose: To describe the clinical, imaging, histopathologic, immunohistochemical, and ultrastructural characteristics of coexistent amyloid and spheroidal degeneration-type deposits in a family with Histidine-626-Arginine Transforming Growth Factor Beta Inducible Gene (H626R TGFBI) corneal stromal dystrophy.

Methods: Retrospective clinical-pathologic and genetic analysis of one family with H626R lattice dystrophy.

Results: The disease showed autosomal dominant inheritance pattern by pedigree analysis. The affected individuals presented in 4th or 5th
decades with progressive visual impairment and recurrent erosions. Ophthalmic examination of the 3 affected family members revealed asymmetric, thick, branching lattice-like deposits, associated with corneal haze. Sequencing of the TFGBI gene revealed a high-penetrance disease causing sequence variation (H626R CAT>CAT heterozygous). Optical coherence tomography demonstrated fusiform, poorly demarcated, hyper-echoic stromal deposits, consistent with amyloid, with focal hypo-echoic central region. Histologic evaluation of the corneal buttons from the 2 affected family members showed stromal fusiiform Periodic acid-Schiff (PAS)-positive, Congo red-positive, birefringent, and keratoepithelin antibody-immunoreactive deposits, consistent with TGFBI amyloid. Few amyloid deposits contained a central nidus of spheroidal degeneration-type material. This material demonstrated autofluorescence, stained with elastic and Masson-trichrome stains, did not stain with PAS or Congo red stains, was non-birefringent, and did not immunoreact with keratoepithelin antibodies. Transmission electron microscopy confirmed the presence of peripheral amyloid fibrils with central electrondense, homogeneous, discrete spheroidal degeneration-type deposits.

**Conclusions:** Presence of spheroidal degeneration-type deposits in a subset of affected patients, the variability in presentation within an individual and between the family members, the predominant anterior corneal stromal location and the non-immunoreactivity of deposits for keratoepithelin suggest that these deposits are degenerative in nature. The deposits may arise from ultraviolet light-altered proteins diffused from the limbus, which form a nidus for mutant keratoepithelin deposition in patients with the late onset H626R lattice dystrophy variant.

**Commercial Relationships:** An-Katrien De Roo, None; Beatrijs Foets, None; Joost J. van den Oord, None

**Support:** PhD fellow for Research Foundation – Flanders (11C7513N)

**Program Number:** 1847 **Poster Board Number:** A0403 **Presentation Time:** 11:00 AM–12:45 PM

**Clinicopathologic Features of Ophthalmic Neoplasms Arising in the Setting of Xeroderma Pigmentosum**

**Maria J. Suarez B, Fausto J. Rodriguez**

Ophthalmic Pathology, Johns Hopkins University, Baltimore, MD.

**Purpose:** To determine the clinical, pathologic and immunohistochemical (IHC) features of neoplasms involving the ocular surface and/or adnexa in three patients satisfying clinical criteria for Xeroderma Pigmentosum (XP).

**Methods:** We retrieved formalin-fixed paraffin-embedded material from tumors involving the ocular surface and ocular adnexa from 3 patients with XP who underwent clinical evaluation at our institution. Clinical information was obtained by retrospective chart review. Histopathological evaluation was performed, as well as immunohistochemistry in all available cases using antibodies directed against the most common mutated proteins in XP patients (XPA, XPC, and XPD). Scoring of nuclear immunoreactivity was performed in 3-tiered scale: 0 = negative staining; 1=weak/focal staining; 2=moderate to strong staining; 3=strong staining.

**Results:** Three (9, 13, 28 years old) patients of African descent with XP (2 males, 1 female) and ocular and adnexal tumors were studied. Patient 1 had two squamous cell carcinomas (SCC) in the conjunctiva (one in situ and one invasive). Patient 2 had invasive basal cell carcinoma (BCC), SCC in situ of the eyelid, and orbital malignant melanoma with recurrence. Patient 3 had invasive SCC of the eyelid. Nuclear expression of XPA, XPC, and XPD proteins in normal eyelid skin, particularly in basal epithelium and adnexal glands, was noted in controls. Nuclear staining for XPD was also present in normal conjunctiva. In patient 1, immunoexpression of XPA and XPC was present in both tumors, while XPD was lost in the invasive (but not in situ) SCC. Conversely, patient 2 had XPA loss in invasive tumors (BCC, melanoma) and retained XPC and XPD. Positive immunoreactivity for XPA, XPC and XPD in SCC in situ was present. Finally, patient 3 showed retained XPA, XPC, and XPD expression in SCC.

**Conclusions:** Our study outlines our early experience with pathology of ocular neoplasms in XP patients. XPC immunoreactivity in all tumors suggests that XPC genetic alterations may not be a common feature in our population. Immunohistochemistry for XPA and XPD
Program Number: 1848 Poster Board Number: A0404
Presentation Time: 11:00 AM–12:45 PM
Novel ultrastructural patterns of corneal immunoglobulin deposition in monoclonal gammopathy of undetermined significance

Andrew A. Kao, Jason Reidy, David S. Chu, Ira J. Udell, Anne Steiner, Carrie Zaslav, Tatyan Milman.

Purpose: To describe two novel ultrastructural patterns of corneal immunoglobulin deposition in monoclonal gammopathy of undetermined significance (MGUS).

Methods: The corneal buttons of two patients with monoclonal gammopathy were studied. Histologic sections of corneal tissue were stained with hematoxylin and eosin, periodic acid-Schiff (PAS), Masson trichrome, and Congo red stains. Immunohistochemistry and in situ hybridization (ISH) studies for immunoglobulin heavy and light chains were performed on the histologic sections. Transmission electron microscopy (TEM) was also performed. Pertinent literature was reviewed.

Results: Patient 1: A 76-year-old woman presented with bilateral corneal haze and vascularization believed to be secondary to old interstitial keratitis. Penetrating keratoplasty was performed. Histologic analysis revealed cosinophilic deposits within the corneal stroma which stained strongly with Masson trichrome. ISH failed to demonstrate the presence of light chains. TEM demonstrated extracellular electron-dense stromal scroll-like deposits ranging in size from 100-300 nm in diameter. Further clinical workup demonstrated MGUS. The patient is being monitored without treatment, with no recurrence noted at 16-month follow-up.

Patient 2: A 53-year-old man presented with bilateral crystalline corneal opacities in the epithelium and superficial stroma in 2008. Serum protein electrophoresis (SPEP) was negative. The haze worsened in 2013 and repeat SPEP showed an M spike, presumed MGUS. Corneal biopsy demonstrated non-birefringent eosinophilic, PAS-positive, and Masson trichrome-positive deposits within the epithelium, Bowman layer, and superficial stroma. The deposits immunoreacted with antibodies to lambda light chains. TEM demonstrated round, electron-dense deposits consistent with immune complexes. Systemic workup including bone marrow biopsy is pending.

Conclusions: To our knowledge, the ultrastructural patterns of large scroll-like deposits and immune complexes have not been previously described in the cornea but have been reported in the kidneys of patients with paraproteinemia. Our findings underscore the importance of careful clinical, histopathologic and ultrastructural evaluation of patients with corneal opacities suggestive of paraproteinemia.

Commercial Relationships: Andrew A. Kao, None; Jason Reidy, None; David S. Chu, None; Ira J. Udell, None; Anne Steiner, None; Carrie Zaslav, None; Tatyan Milman, None

Program Number: 1849 Poster Board Number: A0405
Presentation Time: 11:00 AM–12:45 PM
Fluorescence Microscopy Identification of Retinal Pigment Epithelium-65 and Zonular Ocludens-1 Expression in Spontaneously Differentiated Human Embryonic Stem Cell derived Retinal Pigment Epithelium Cells


Purpose: To evaluate cellular expression profiles of retinal pigment epithelium-65 (RPE65) and zonular ocludens-1 (ZO-1) markers during spontaneous differentiation human embryonic stem cell into retinal pigment epithelial cells (hESC-RPE)

Methods: Human embryonic stem cells (hESC), from the WA09-DL-11 feeder dependent line, were removed from liquid nitrogen and grown on a confluent layer of inactivated mouse embryonic fibroblast. Differentiated pigmented embryoid body (EB) clusters were dissected from undifferentiated hESC colonies. After dissection, EBs were isolated onto 6-well gelatin coated plates for further monolayer expansion into hESC-RPE cells. Confluent monolayers were passaged 2–3 weeks following EB isolation and plated onto gelatin-coated slides. Each slide was placed into a 10 mm petri dish filled with RPE maintenance media and allowed to grow to either 7, 21, or 35 days post passage. Slides were extracted on designated time points and prepared for immunohistochemistry with antibodies targeted to RPE65 and ZO-1. Immunofluorescence was performed under 10x magnification on an inverted Olympus IX51-IX2-SL microscope with Olympus U-RFL-T fluorescence lamp.

Results: Day seven following hESC-RPE precursor cell plating showed no evidence of RPE65 or ZO-1 expression. Two weeks later on day 21, maturation of hESC-RPE precursor cells demonstrated an enhanced fluorescence of RPE65 and a slight fluorescence increase in ZO-1 expression. Four weeks after precursor cell plating, fluorescence intensity for both RPE65 and ZO-1 was more intense than the prior two time points.

Conclusions: This study shows enhanced in vitro cellular expression patterns of RPE65 and ZO-1 during differentiation of hESC-RPE precursor cells into a more mature state. Based on the above findings, precursor hESC-RPE cells demonstrate RPE marker patterns between one to three weeks after plating. This information can assist with therapeutic implementation especially when attempting to identify points of hESC-RPE precursor maturation.

Commercial Relationships: Lee R. Ferguson, None; K V Chalam, None

Program Number: 1850 Poster Board Number: A0406
Presentation Time: 11:00 AM–12:45 PM
Alzheimer-induced changes in biomarkers in the Human Lateral Geniculate Nucleus

Elizabeth Couser, Steven L. Bernstein. Gerontology Doctoral Program, University of Maryland, Baltimore, Baltimore, MD; Ophthalmology & Visual Sciences, University of Maryland School of Medicine, Baltimore, MD.

Purpose: While Alzheimer’s disease (AD) patients are known to experience histological retinal changes, the thalamic intermediaries connecting eye and cortex have been understudied. We wanted to examine whether Alzheimer’s disease (AD) biomarkers are expressed in the normal human lateral geniculate nucleus (LGN) and whether AD alters the presence of these markers. We also wanted to determine whether these markers are expressed in pre-clinical AD.

Methods: Following IRB approval, we obtained human tissue samples from the Maryland Brain and Tissue Bank. These included normal, pre-clinical, and severe AD. We immunohistochemically evaluated human LGN for the expression of both AD markers.

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(phosphorylated tau, amyloid precursor protein (APP) and amyloid-β (Aβ)) and inflammation using standard immunohistochemistry (IHC) procedures. Cellular inflammation was compared using IBA1. Slides were analyzed using a confocal fluorescent microscope and Fluoview Software.

**Results:** While normal tissue showed minimal expression of AD biomarkers, there was a progressive increase in Tau, Aβ, APP, and inflammation in the lateral geniculate nucleus through the different stages of AD severity. Interestingly, the inflammatory response and deposits of AD biomarkers were shown in significant amounts in the pre-clinical AD samples of the LGN.

**Conclusions:** The LGN-thalamic structure shows AD-induced alterations as the disease progresses and very early in the disease process. This may result in a decreased ability to process visual information, and visual problems. The presence of inflammation and AD-related biomarkers in pre-clinical AD patients suggests that for at least some older adults, changes in visual processing ability and speed may be due to AD onset, and not normal age-related visual decline.

**Commercial Relationships:** Elizabeth Couser, None; Steven L. Bernstein, None

**Program Number:** 1851 **Poster Board Number:** A0407  
**Presentation Time:** 11:00 AM – 12:45 PM  
**Müller Cell Glial Fibrillary Acidic Protein (GFAP) Upregulation in Experimental Glaucoma is not dependent on the Presence of Retinal Ganglion Cells (RGCs)**

**Methods:** Immunohistochemistry for GFAP was performed on the retinas of both eyes of 13 monkeys. In all of the animals, the right eye was the experimental eye and the left eye was the untreated control. 6 cynomolgus macaques had glaucoma induced by laser trabecular destruction (LTD) from 3 to 9 years prior to sacrifice. The mean IOPs during the last 14 months of life varied from 23 to 54 mmHg in the treated eyes (43 mean for all animals). 4 cynomolgus macaques had inferior hemiretinal endodiathermy axotomy (HEA) either 3 or 4 months prior to sacrifice with no elevation in IOP (Dashek et al, IOVS, 2013;54:3479). 3 rhesus macaques had HEA axotomy and 9.5 months later underwent LTD (mean IOP varied from 34 to 56 mmHg) and were sacrificed 4.5 months after LTD.

**Results:** Although the retinal astrocytes and optic nerve oligodendrocytes were strongly positive for GFAP, there was little or no upregulation of GFAP in the Müller cells in any of the 6 eyes with chronic glaucoma. Likewise, there was no upregulation of GFAP in the Müller cells of any of the 4 eyes that underwent HEA alone. However, there was marked Müller cell GFAP upregulation in both the superior (no axotomy) and inferior (axotomy) areas of all 3 eyes that had HEA plus 4.5 months of experimental glaucoma.

**Conclusions:** Müller cell GFAP upregulation is not dependent on the presence of RGCs since upregulation occurred even though RGCs were essentially absent from the axotomized areas of retina in the 3 HEA animals with elevated IOP. However, elevated IOP alone is not a sufficient condition for sustained Müller cell GFAP upregulation because it was not readily apparent in any of the 6 eyes with chronic glaucoma. One possibility is that Müller cell GFAP upregulation is the result of retinal ischemia, such as from decreased chorioidal blood flow. Compensatory mechanisms, e.g. increased blood flow or decreased retinal oxygen need due to retinal cell death and/or lowered metabolism, may have allowed the Müller cell GFAP to return to nearly normal levels in the eyes with chronic glaucoma.

**Commercial Relationships:** Jeffrey C. Ockuly, None; Charlene B Y. Kim, None; Brian J. Christian, None; Mélissa C. De Lambera, None; T Michael Nork, None

**Support:** NIH Grant P30 EY016665, Research to Prevent Blindness, The Wisconsin National Primate Research Center P51RR00167/ P51OD011106

**Program Number:** 1852 **Poster Board Number:** A0408  
**Presentation Time:** 11:00 AM – 12:45 PM  
**Elevated photoreceptor COX-2 expression correlates with aging retinas**

**Purpose:** Elevated COX-2 is often associated with inflammation and neoplasia, published reports have shown COX-2 to be expressed in normal tissue. Our aim was to evaluate expression of COX-2 in all layers of the normal human retina and determine whether correlations with age or gender exist.

**Methods:** 130 formalin-fixed, paraffin-embedded normal human eyes were selected to investigate the expression of COX-2. Immunohistochemistry was performed using anti-human COX-2 antibody. Immunostaining was classified based on intensity (negative=0, weak=1, strong=2) and extent (negative=0, staining ≤50% of cells=1, staining >50% of cells=2). An immunoreactive score (IRS) was calculated to describe the expression of COX-2 using the following equation: 2 x expression x intensity. Results were expressed in the following manner: 0–2=negative, 3–4=weak, ≥5=strong. Logistic regression analysis was conducted to estimate the association between age and staining score of any layer. Linear regression analysis was used to determine possible correlations between IRS and time elapsed between death and enucleation or enucleation and tissue processing p-value <0.05 was considered statistically significant.

**Results:** Of the 130 eyes evaluated, 72 were from female donors, 53 from male donors, and 5 from donors with no gender information. Mean age was 62.1 years. A total of 78 cases had RPE and 66 had sufficient neurosensory retina for evaluation. The number of cases with positive COX-2 expression by retinal layer was: retinal pigmented epithelium (RPE): 61/78; nerve fiber layer: 33/66; ganglion cell layer: 58/66; inner plexiform layer: 56/66; outer plexiform layer: 31/66; outer nuclear layer: 31/66; photoreceptors: 55/66. COX-2 expression in the photoreceptors was significantly correlated with older donor age (p=0.045). COX-2 IRS was strong in the ganglion cell, photoreceptor and RPE layers. No significant correlations were found between IRS and time elapsed between death and enucleation or IRS and time elapsed between enucleation and tissue processing.

**Conclusions:** COX-2 is expressed throughout the normal human retina with strong expression on ganglion cell, photoreceptor and RPE layers. Its expression in photoreceptors is significantly correlated with older age. These results demonstrate that consideration of a role for COX-2 in normal retinal physiology is warranted, particularly when anti-COX-2 medications are being prescribed.

**Commercial Relationships:** Carlos Quezada1, 2, Patrick Logan, Ana Beatriz T. Dias, Francisco Ceballos, Lisa Jagan, Tiago Broccoli, Miguel N. Burnier

1Ophthalmology & Pathology, The Henry C. Witelson Ocular Pathology Laboratory, McGill University, Montreal, QC, Canada; 2California Retina Consultants, Santa Barbara, CA.

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DISTINCT RETINAL LAYERS

SIRTUINS ARE DIFFERENTIALLY EXPRESSED IN

Natalía Vilà, Pablo Zoroquinai, Shawn C Maloney, Ana Beatriz T. Dias, Emilia Antecka, Miguel N. Burnier. Ophthalmology - Ocular Pathology, McGill University, Montreal, QC, Canada.

Purpose: While recent studies have indicated a role for Sirtuins (SIRT) in biological processes, including metabolic diseases, cancer, diabetes and aging, the exact nature of SIRT functions has not been elucidated. Moreover, their function and expression in normal ocular tissues remain unknown. The aim of this study is to evaluate the expression of all sirtuin proteins (SIRT1-7) in normal human retinas.

Methods: Twenty-three formalin-fixed, paraffin-embedded normal donor eyes (mean age = 72 +/- 21.7 years), were evaluated in this study. Immunohistochemistry was performed on serial sections of all eyes with antibodies against each of the seven individual sirtuins (SIRT1-7). Staining was graded semi-quantitatively in the macula area and peripheral retina based on the intensity (negative=0, weak=1, strong=2) and extent (negative=0, staining ≤50% of cells=1, staining >50% of cells=2). A combined score was calculated to describe the expression for each sirtuin using the following equation: 2 x expression x intensity. Results were expressed in the following manner: 0 to 2=negative, 3 to 4= weak expression, ≥5 = strong expression.

Results: All sirtuins were expressed in all of the studied retinas; however, the staining score differed for each sirtuin across the various retinal layers assessed. The retinal pigment epithelium (RPE) expressed SIRT-4, 6 and 7. SIRT-6 was strongly positive only in the macula, and both SIRT-4 and -7 were also strongly positive in the macula and peripheral retina. The inner nuclear layer (INL) weakly expressed SIRT-3 throughout the retina. The outer nuclear layer (ONL) was the sole structure that was negative for all sirtuins. No significant differences were found between macular and peripheral retina in the same layer, except for SIRT-6 in RPE, which was strongly expressed in the macula while negative in the peripheral retina (p<0.05).

Conclusions: Our data provides an overview of the expression of sirtuins in normal human retinas. SIRT-3 was the only sirtuin protein found in the inner nuclear layer, while no sirtuins were expressed in the outer nuclear layer of the retina. These results serve as a foundation for further research into the roles of sirtuins in normal and diseased retina.

Commercial Relationships: Natalía Vilà, None; Pablo Zoroquinai, None; Shawn C Maloney, None; Ana Beatriz T. Dias, None; Emilia Antecka, None; Miguel N. Burnier, None

Expression of amyloid and tau proteins in the Octodon degus retina

Monica L. Acosta1, Lily Chang1, Alvaro Ardiles2, Adrian Palacios3.
1Optometry & Vision Science, The University of Auckland, Auckland, New Zealand; 2Centro Interdisciplinario de Neurociencias, Universidad de Valparaiso, Valparaiso, Chile.

Purpose: To determine whether the Octodon degus, an animal model of Alzheimer’s disease (AD) expresses amyloid and tau proteins indicative of AD in the eye as a function of development.

Methods: The retina from developing Octodon degus aged less than 6 months (2-6 months-old; n=6) and adults older than 5 years (n=7) were employed. Eyes were collected immediately post-mortem and immersion fixed in 4% paraformaldehyde in PBS (pH 7.4) for over an hour. Immunohistochemical methods were applied to cross-sections of the retina and retinal whole mounts. Horseradish peroxidase (HRP-DAB) staining was carried out on similar sections. The retina was immunolabeled against the major AD proteins using antibodies against amyloid-beta (APP)4, Aβ peptide (Aβ4G8, Aβ6E10), Aβ oligomers (A11), tau (Tau5A6) and hyper-phosphorylated tau (PHF-tau). The area occupied by the antibody mark in young and old retina was quantified. Congo red staining was used to determine the presence of Aβ plaques.

Results: AD proteins were predominantly expressed in the ganglion cell layer in the adult but not in the young retina. Tau and hyper-phosphorylated tau were expressed in the central and peripheral retina. Normal amyloid proteins were expressed in both young and old retina while Aβ oligomers were only seen in old animals central retina. Congo red staining revealed no apple-green birefringence.

Conclusions: There was an age-related expression of AD proteins in O. degus eyes and the existence of common factors in the ocular and brain tissues involved in AD etiology/pathogenesis. This further supports the idea that non-invasive eye tests could be developed for early AD diagnosis and that O. degus is a suitable model for developing and validating diagnostic tests.

Commercial Relationships: Monica L. Acosta, None; Lily Chang, None; Alvaro Ardiles, None; Adrian Palacios, None

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