Drug treatment


Treating the untreatable patient: current options for the management of treatment-resistant neovascular age-related macular degeneration.

Broadhead GK, Hong T, Chang AA.

Abstract: Anti-vascular endothelial growth factor (anti-VEGF) agents represent the current standard of care for neovascular age-related macular degeneration (nAMD). Although effective in a majority of cases, a significant proportion of patients have persisting retinal exudation despite regular anti-VEGF therapy. This exudation is considered to produce poorer visual outcomes in these patients. Some of these patients may have misdiagnosed nAMD variants such as polypoidal choroidal vasculopathy; however, the majority of these eyes have what has been termed treatment-resistant nAMD. Currently, the best way to care for these patients is uncertain. Here, we review the evidence for different approaches to the management of treatment-resistant nAMD, including high-dose anti-VEGF therapy, combination regimes and switching of anti-VEGF agents, and discuss possible therapeutic approaches for patients with treatment-resistant nAMD.

PMID: 24925048 [PubMed - as supplied by publisher]


Delayed onset panuveitis following intravitreal aflibercept injection.

Glading JA, Lake SR, Craig JE, Supramaniam D.

Abstract: Aflibercept has been listed on the Australian Pharmaceutical Benefit Scheme for the past year for neovascular age-related macular degeneration. Since that time there have not been any reports of delayed onset panuveitis. We present two cases of anterior and posterior uveitis that have occurred 4 weeks or more after first intravitreal injection of aflibercept. Both patients had received other vascular endothelial growth factor inhibitors prior to aflibercept administration without signs of inflammation and both cases had sterile endophthalmitis. On resolution of the inflammation the patients were recommenced on ranibizumab without further incident.

PMID: 24920511 [PubMed - in process]
RANIBIZUMAB IN PREPROLIFERATIVE (ISCHEMIC) CENTRAL RETINAL VEIN OCCLUSION: The Rubeosis Anti-VEGF (RAVE) Trial.

Brown DM, Wykoff CC, Wong TP, Mariani AF, Croft DE, Schuetzle KL; for the RAVE Study Group.

PURPOSE: To analyze the efficacy and safety of ranibizumab in eyes with preproliferative (ischemic) central retinal vein occlusion.

METHODS: In this prospective, phase I/II, open-label clinical trial, eyes at high risk of neovascular complications were identified; all eyes met ≥3 of 4 high-risk criteria: 1) the best-corrected visual acuity being ≤20/200, 2) loss of the 1-2e isopter on Goldmann visual field, 3) relative afferent pupillary defect being ≥0.9 log units, and 4) electroretinogram B-wave reduction to ≤60% of the corresponding A-wave. Monthly intravitreal ranibizumab treatment for 9 months, monthly monitoring for 3 months, and then monthly examination with pro re nata retreatment on evidence of disease activity for 24 months were performed. Therefore, the total study duration was 36 months.

RESULTS: The main outcome measures were mean change in the best-corrected visual acuity and central macular thickness by optical coherence tomography, proportion of patients with neovascular complications, and the incidence and severity of ocular and nonocular adverse events. Twenty patients were enrolled in the Rubeosis Anti-VEGF trial, and the mean number of intravitreal treatments administered through Months 24 and 36 were 14.1 and 17.2, respectively. The mean best-corrected visual acuity letters gained were +21.1 and +21.4 at 9 and 36 months, respectively. The mean central macular thickness increased -294 μm from baseline after 9 monthly treatments. Subsequently, after 3 months of observation, the mean central macular thickness then improved -191 μm at Month 36 compared with Month 12. Nine patients developed neovascular complications, being diagnosed after a mean of 24-month follow-up (range, 3-44 months), with 2 patients developing neovascularization after completion of the 36-month trial endpoint (at Months 42 and 44 after study enrollment).

CONCLUSION: Intravitreal ranibizumab therapy can improve retinal anatomy and vision in eyes with severe central retinal vein occlusion. Despite significant clinical benefit with antivascular endothelial growth factor therapy, the risk of neovascular complications was not ameliorated by vascular endothelial growth factor blockade, but was merely delayed.

PMID: 24914476 [PubMed - as supplied by publisher]

Anti-VEGF Therapy for Diabetic Macular Edema.

Stewart MW.

Abstract: Vascular endothelial growth factor (VEGF) plays a pivotal role in the development of diabetic macular edema (DME), the leading cause of vision loss among working-aged individuals. A decade of clinical trials demonstrated that drugs that bind soluble VEGF restore the integrity of the blood-retinal barrier, resolve macular edema, and improve vision in most patients with DME. Four drugs (pegaptanib, ranibizumab, bevacizumab, and aflibercept) effectively treat DME when administered by intravitreal injections. Only ranibizumab has received U.S. Food and Drug Administration (FDA) approval for DME, but bevacizumab is commonly used off-label, and an FDA application for aflibercept is pending. Effective treatment requires repeated injections, although recent data suggest that the treatment burden diminishes after 1 year. Intravitreal therapy is generally safe, although the incidence of systemic thromboembolic events varies among trials.

PMID: 24919750 [PubMed - in process]
Other treatment & diagnosis


The Evonik-Mainz-Eye-Care-Study (EMECS): Design and Execution of the Screening Investigation.


PURPOSE: To determine if screening for major ophthalmological diseases is feasible within the frame of routine occupational medicine examinations in a large working population.

METHODS: 13037 employees of Evonik Industries aged 40 to 65 years were invited to be screened for major ophthalmological diseases (glaucoma, age related macular degeneration and diabetic retinopathy between June 2007 and March 2008 within an extended setting of occupational medicine. Ophthalmological examinations consisted of visual acuity, objective refraction, pachymetry, tonometry, perimetry (frequency doubling technology), confocal scanning laser ophthalmoscopy and digital fundus photography. Participants responded to a questionnaire addressing history of ocular and general diseases and social history.

RESULTS: 4183 participants (961 female and 3222 male) were examined at 13 different sites. Response rates for eligible persons at those sites ranged from 17.9 to 60.5% but were in part limited by availability of examination slots. Average age of participants was 48.4±5.4 years (mean ± SD). 4147 out of 4183 subjects (99.1%) had a visual acuity ≥0.5 in the better eye and 3665 out of 4183 (87.6%) subjects had a visual acuity ≥0.8 in the better eye. 1629 participants (38.9%) had previously not been seen by an ophthalmologist at all or not within the last three years.

CONCLUSION: This article describes the study design and basic characteristics of study participants within a large occupational medicine based screening study for ophthalmological diseases. Response rates exceeded expectations and were limiting examination capacity. Meaningful data could be obtained for almost all participants. We reached participants who previously had not received ophthalmic care. Thus, ophthalmological screening appears to be feasible within the frame of routine occupational medicine examinations.

PMID: 24915063 [PubMed - in process]


Choroidal Haller's and Sattler's Layer Thickness Measurement Using 3-Dimensional 1060-nm Optical Coherence Tomography.


OBJECTIVES: To examine the feasibility of automatically segmented choroidal vessels in three-dimensional (3D) 1060-nmOCT by testing repeatability in healthy and AMD eyes and by mapping Haller's and Sattler's layer thickness in healthy eyes.

METHODS: Fifty-five eyes (from 45 healthy subjects and 10 with non-neovascular age-related macular degeneration (AMD) subjects) were imaged by 3D-1060-nmOCT over a 36°x36° field of view. Haller's and Sattler's layer were automatically segmented, mapped and averaged across the Early Treatment Diabetic Retinopathy Study grid. For ten AMD eyes and ten healthy eyes, imaging was repeated within the same session and on another day. Outcomes were the repeatability agreement of Haller's and Sattler's layer thicknesses in healthy and AMD eyes, the validation with ICGA and the statistical analysis of the effect of age and axial eye length (AL) on both healthy choroidalsublayers.

RESULTS: The coefficients of repeatability for Sattler's and Haller's layers were 35% and 21% in healthy
eyes and 44% and 31% in AMD eyes, respectively. The mean±SD healthy central submacular field thickness for Sattler's and Haller's was 87±56 µm and 141±50 µm, respectively, with a significant relationship for AL (P<.001).

CONCLUSIONS: Automated Sattler's and Haller's thickness segmentation generates rapid 3D measurements with a repeatability corresponding to reported manual segmentation. Sublayers in healthy eyes thinned significantly with increasing AL. In the presence of the thinned Sattler's layer in AMD, careful measurement interpretation is needed. Automatic choroidal vascular layer mapping may help to explain if pathological choroidal thinning affects medium and large choroidal vasculature in addition to choriocapillaris loss.

PMID: 24911446 [PubMed - in process]


Demonstration of a broad band spectral head-mounted display with freeform mirrors.

Pan JW, Che-Wen C, Huang KD, Wu CY.

Abstract: It has been demonstrated that electrical stimulation of the retina can produce visual perception for blind patients suffering from macular degeneration and retinitis pigmentosa. In order to let the retinal chip generate enough electrical stimulation, the near infrared ray source is added to enhance the stimulation current. However, it is a challenge to design a head-mounted display (HMD) that covers both visible and infrared rays. Since the HMD system covers such a broad spectral band, large color aberrations will be induced. In order to eliminate these large aberrations, a mirror system is adopted that will create a no color aberration system. We also use two freeform mirrors (FFMs) to reduce residual aberrations such as spherical aberrations and coma. The FFMs serve as the near-eye viewing optics that magnifies the image which is displayed through a microdisplay. Based on a 0.61 in. microdisplay, the HMD system demonstrates a diagonal field of view (FOV) of 30 degree and an f/# of 3.75, with an exit pupil diameter of 8 mm and eye clearance of 15mm.

PMID: 24921474 [PubMed - in process]

Pathogenesis


Choriocapillaris breakdown precedes retinal degeneration in age-related macular degeneration.

Biesemeier A, Taubitz T, Julien S, Yoeruek E, Schraermeyer U.

Abstract: This work presents a combined light and electron microscopical approach to investigate the initial breakdown of the retinal pigment epithelium (RPE) and choriocapillaris (CC) in age-related macular degeneration (AMD). Perimacular sections of 12 dry and wet AMD eyes (82 ± 15 years) and 7 age-matched controls (75 ± 10 years) without retinal pathology were investigated. Disease progression was classified into 5 stages of retinal degeneration to investigate the concurrent CC breakdown. Special emphasis was laid on transitions where intact CC-RPE-retina complexes went over into highly atrophied areas. AMD sections showed elevated loss of photoreceptors, RPE and CC (p < 0.01), and thickened Bruch's membrane with increased basal laminar and linear deposits compared with controls. Up to 27% of the CC was lost in controls although RPE and retina were still intact. This primary loss of CC further increased with AMD (up to 100%). The data implicate that CC breakdown already occurs during normal aging and precedes degeneration of the RPE and retina with AMD, defining AMD as a vascular disease. Particular attention should be given to the investigation of early AMD stages and transitional stages to the late stage.
that reveal a possible sequence of degenerative steps with aging and AMD.

PMID: 24925811 [PubMed - as supplied by publisher]


Polypoidal choroidal vasculopathy and history of central serous chorioretinopathy.

Toyama T, Ohtomo K, Noda Y, Ueta T.

Purpose: To evaluate the possible causative role of central serous chorioretinopathy (CSC) in the development of exudative age-related macular degeneration (AMD).

Methods: In a cross-sectional study at an institutional setting, 150 control subjects who had senile cataract or nasolacrimal duct stenosis and who were older than 50 years were enrolled. The background data for 89 patients with typical AMD (tAMD) and 138 patients with polypoidal choroidal vasculopathy (PCV) were used for comparison. Their medical records were taken for history of CSC, hypertension, systemic steroid use, and smoking. The fundus was also evaluated for signs of atrophic retinal pigment epithelial (RPE) tract and for focal photocoagulation scars in the macula.

Results: After adjusting for age, gender, and history of hypertension, systemic steroid use, and smoking, history of CSC was significantly more frequent (P<0.0001) in patients with PCV (15 patients, 10.9%) compared with patients with tAMD (2 patients, 2.2%) or control subjects (0 patients). On fundoscopy, an atrophic RPE tract (seven patients) or a focal photocoagulation scar (one patient) was observed only in patients with PCV (eight patients, 5.8%), and the frequency was statistically significant compared with that with tAMD (P=0.0143) or control subjects (P=0.0143). The laterality of CSC and AMD involved the same eye in 9 of 10 patients among those who had unilateral AMD and a reported unilateral CSC history.

Conclusion: A history of CSC may be a predisposing factor for the development of PCV in the Japanese population.

PMID: 24924443 [PubMed - as supplied by publisher]


Estrogen Signalling in the Pathogenesis of Age-Related Macular Degeneration.


Abstract: Age-related macular degeneration (AMD) is a multifactorial eye disease that is associated with aging, family history, smoking, obesity, cataract surgery, arteriosclerosis, hypertension, hypercholesterolemia and unhealthy diet. Gender has commonly been classified as a weak or inconsistent risk factor for AMD. This disease is characterized by degeneration of retinal pigment epithelial (RPE) cells, Bruch's membrane, and choriocapillaris, which secondarily lead to damage and death of photoreceptor cells and central visual loss. Pathogenesis of AMD involves constant oxidative stress, chronic inflammation, and increased accumulation of lipofuscin and drusen. Estrogen has both anti-oxidative and anti-inflammatory capacity and it regulates signaling pathways that are involved in the pathogenesis of AMD. In this review, we discuss potential cellular signaling targets of estrogen in retinal cells and AMD pathology.

PMID:24911983 [PubMed - as supplied by publisher]


Origins and consequences of hyperosmolar stress in retinal pigmented epithelial cells.
Willermain F, Libert S, Motulsky E, Salik D, Caspers L, Perret J, Delporte C.

Abstract: The retinal pigmented epithelium (RPE) is composed of retinal pigmented epithelial cells joined by tight junctions and represents the outer blood-retinal barrier (BRB). The inner BRB is made of endothelial cells joined by tight junctions and glial extensions surrounding all the retinal blood vessels. One of the functions of the RPE is to maintain an osmotic transepithelial gradient created by ionic pumps and channels, avoiding paracellular flux. Under such physiological conditions, transcellular water movement follows the osmotic gradient and flows normally from the retina to the choroid through the RPE. Several diseases, such as diabetic retinopathy, are characterized by the BRB breakdown leading to leakage of solutes, proteins, and fluid from the retina and the choroid. The prevailing hypothesis explaining macular edema formation during diabetic retinopathy incriminates the inner BRB breakdown resulting in increased osmotic pressure leading in turn to massive water accumulation that can affect vision. Under these conditions, it has been hypothesized that RPE is likely to be exposed to hyperosmolar stress at its apical side. This review summarizes the origins and consequences of osmotic stress in the RPE. Ongoing and further research advances will clarify the mechanisms, at the molecular level, involved in the response of the RPE to osmotic stress and delineate potential novel therapeutic targets and tools.

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Human Retinal Transmitochondrial Cybrids with J or H mtDNA Haplogroups Respond Differently to Ultraviolet Radiation: Implications for Retinal Diseases.


BACKGROUND: It has been recognized that cells do not respond equally to ultraviolet (UV) radiation but it is not clear whether this is due to genetic, biochemical or structural differences of the cells. We have a novel cybrid (cytoplasmic hybrids) model that allows us to analyze the contribution of mitochondrial DNA (mtDNA) to cellular response after exposure to sub-lethal dose of UV. mtDNA can be classified into haplogroups as defined by accumulations of specific single nucleotide polymorphisms (SNPs). Recent studies have shown that J haplogroup is high risk for age-related macular degeneration while the H haplogroup is protective. This study investigates gene expression responses in J cybrids versus H cybrids after exposure to sub-lethal doses of UV-radiation.

METHODOLOGY/PRINCIPAL FINDINGS: Cybrids were created by fusing platelets isolated from subjects with either H (n=3) or J (n=3) haplogroups with mitochondria-free (Rho0) ARPE-19 cells. The H and J cybrids were cultured for 24 hours, treated with 10 mJ of UV-radiation and cultured for an additional 120 hours. Untreated and treated cybrids were analyzed for growth rates and gene expression profiles. The UV-treated and untreated J cybrids had higher growth rates compared to H cybrids. Before treatment, J cybrids showed lower expression levels for CFH, CD55, IL-33, TGF-A, EFEMP-1, RARA, BCL2L13 and BBC3. At 120 hours after UV-treatment, the J cybrids had decreased CFH, RARA and BBC3 levels but increased CD55, IL-33 and EFEMP-1 compared to UV-treated H cybrids.

CONCLUSION/SIGNIFICANCE: In cells with identical nuclei, the cellular response to sub-lethal UV-radiation is mediated in part by the mtDNA haplogroup. This supports the hypothesis that differences in growth rates and expression levels of complement, inflammation and apoptosis genes may result from population-specific, hereditary SNP variations in mtDNA. Therefore, when analyzing UV-induced damage in tissues, the mtDNA haplogroup background may be important to consider.

PMID: 24919117 [PubMed - in process]
Circadian Rhythm Disorders and Melatonin Production in 127 Blind Women with and without Light Perception.

Flynn-Evans EE, Tabandeh H, Skene DJ, Lockley SW.

Abstract: Light is the major environmental time cue that synchronizes the endogenous central circadian pacemaker, located in the suprachiasmatic nuclei of the hypothalamus, and is detected exclusively by the eyes primarily via specialized non-rod, non-cone ganglion cell photoreceptors. Consequently, most blind people with no perception of light (NPL) have either nonentrained or abnormally phased circadian rhythms due to this inability to detect light. Conversely, most visually impaired participants with some degree of light perception (LP) exhibit normal entrainment, emphasizing the functional separation of visual and "nonvisual" photoreception. The aims of the study were to identify the prevalence of circadian disorders in blind women, with the further aim of examining how eye disease may relate to the type of circadian disorder. Participants (n = 127, age 50.8 ± 13.4 years) completed an 8-week field study including daily sleep diaries and sequential 4 to 8 hourly urine collections over 48 h on 2 to 3 occasions separated by at least 2 weeks. Circadian type was determined from the timing and time course of the melatonin rhythm measured by cosinor-derived urinary 6-sulfatoxymelatonin rhythm peak. Of the participants with NPL (n = 41), the majority were abnormally phased (24%) or nonentrained (39%), with 37% classified as normally entrained. Of the participants with LP (n = 86), the majority were normally entrained (69%). Eighteen LP participants (21%) were abnormally phased (8 advanced, 10 delayed). Nine LP participants (10%) were nonentrained. The eye conditions most associated with abnormal phase and/or nonentrained circadian rhythms were bilateral enucleation (67%) and retinopathy of prematurity (57%). By contrast, 84% of participants with retinitis pigmentosa and 83% of those with age-related macular degeneration were normally entrained. These findings suggest that the etiology of blindness in addition to LP status is related to an individual's ability to process the circadian light signal.

PMID: 24916394  [PubMed - as supplied by publisher]

Epidemiology


Drusen and Photoreceptor Abnormalities in African-Americans with Intermediate Non-neovascular Age-related Macular Degeneration.


Abstract Purpose/Aim: To investigate the relationship of drusen and photoreceptor abnormalities in African-American (AA) patients with intermediate non-neovascular age-related macular degeneration (AMD).

Materials and methods: AA patients with intermediate AMD (n = 11; age 52-77 years) were studied with spectral-domain optical coherence tomography. Macular location and characteristics of large drusen (≥125 µm) were determined. Thickness of photoreceptor laminae was quantified overlying drusen and in other macular regions. A patient with advanced AMD (age 87) was included to illustrate the disease spectrum.

Results: In this AA patient cohort, the spectrum of changes known to occur in AMD, including large drusen, sub-retinal drusenoid deposits and geographic atrophy, were identified. In intermediate AMD eyes (n = 17), there were 183 large drusen, the majority of which were pericentral in location. Overlying the drusen there was significant thinning of the photoreceptor outer nuclear layer (termed ONL+) as well as the inner and outer segments (IS + OS). The reductions in IS + OS thickness were directly related to ONL+ thickness. In a fraction (~8%) of paradrusen locations with normal lamination sampled within ~280 µm of peak drusen height, ONL+ was significantly thickened compared to age and retinal-location-matched normal values.
Topographical maps of the macula confirmed ONL thickening in regions neighboring and distant to large drusen.

Conclusions: We confirm there is a pericentral distribution of drusen across AA-AMD maculae rather than the central localization in Caucasian AMD. Reductions in the photoreceptor laminae overlying drusen are evident. ONL+ thickening in some macular areas of AA-AMD eyes may be an early phenotypic marker for photoreceptor stress.

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**Diet & lifestyle**

*Optom Vis Sci. 2014 Jun 12. [Epub ahead of print]*

**Patient Tobacco Use in Optometric Practice: A Canada-Wide Study.**


PURPOSE: A national census survey of optometrists in Canada measured knowledge of ocular diseases associated with smoking cigarettes and current practice behaviors related to addressing tobacco use with patients, including prevention and cessation. Optometrists were also asked to identify tools to assist addressing tobacco use with patients.

METHODS: An online bilingual (English/French) survey was developed and an e-mail with a link to the survey was sent to all 4528 optometrists registered in Canada. No participation incentives were provided. Frequency data were tabulated for survey items. Logistic regression models were fit to understand respondent characteristics associated with discussing tobacco use prevention and cessation with patients.

RESULTS: The response rate was 19% (850 responses). Almost all respondents (98%) believed that smoking cigarettes was a risk factor for developing age-related macular degeneration; approximately half (55%) assessed the smoking status of patients during their initial visit; 7% reported that they discussed the benefits of tobacco use prevention with patients younger than 19 years; and 33% reported that they always or regularly assess their patients’ interest in quitting smoking. Respondents who completed the survey in English were more likely (odds ratio, 2.4; 95% confidence interval, 1.01 to 5.65) to deliver prevention messaging, compared with respondents who completed the survey in French. Male respondents were less likely to assess patients’ interest in quitting (odds ratio, 0.7; 95% confidence interval, 0.50 to 0.97) than female respondents. Most respondents (90%) were interested in a continuing education program about the impact of smoking on vision and eye health as well as strategies for discussing tobacco cessation and prevention.

CONCLUSIONS: Optometrists are aware of the impact of smoking on ocular health; however, most respondents do not systematically engage in tobacco use prevention and cessation practices. Providing optometrists with tools, including continuing education, may help support patient conversations about the risks of tobacco use and improve public health.

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**The prevalence of anxiety and depression in people with age-related macular degeneration: a systematic review of observational study data.**

Dawson SR, Mallen CD, Gouldstone MB, Yarham R, Mansell G.

BACKGROUND: Comorbid mental health problems have been shown to have an adverse effect on the
quality of life of people with common eye disorders. This study aims to assess whether symptoms of anxiety and/or depression are more prevalent in people with age-related macular degeneration (AMD) than in people without this condition.

METHODS: A systematic search of electronic databases (Medline, CINAHL, EMBASE, PsycINFO) from inception to February 2012 was conducted to identify studies of AMD populations which measured symptoms of anxiety and/or depression. Reference checking of relevant articles was also performed. Data on the study setting, prevalence and how anxiety and depression were measured were extracted from the papers. Critical appraisal was performed using the Critical Appraisal Skills Programme (CASP) tools.

RESULTS: A total of 16 papers were included in the review, from an original search result of 597. The prevalence estimates, taken from nine cross-sectional and cohort studies, ranged from 15.7%-44% for depressive symptoms and 9.6%-30.1% for anxiety symptoms in people with AMD. The seven case-control studies found that people with AMD were more likely to experience symptoms of depression compared with those without AMD, but not more likely to experience symptoms of anxiety.

CONCLUSIONS: Overall, the evidence suggests that symptoms of depression are more prevalent amongst AMD populations than anxiety symptoms. The heterogeneity of the studies included in this review means that it is difficult to draw strong conclusions as to the true estimates of depression and anxiety symptoms in AMD populations and prevented formal meta-analysis. Further research which specifies clinical anxiety and gives clear definitions as to the type of AMD being investigated is required.

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