

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term "macular degeneration".

If you have not already subscribed, please email Rob Cummins at research@mdfoundation.com.au with 'Subscribe to MD Research News' in the subject line, and your name and address in the body of the email.

You may unsubscribe at any time by an email to the above address with your 'unsubscribe' request.

Drug treatment

Retina. 2013 Mar 27. [Epub ahead of print]

A 12-MONTH PROSPECTIVE TRIAL OF INJECT AND EXTEND REGIMEN FOR RANIBIZUMAB TREATMENT OF AGE-RELATED MACULAR DEGENERATION.

Toalster N, Russell M, Ng P.

*School of Medicine, University of Queensland, Queensland, Australia; †Eye Centre, Southport, Queensland, Australia; ‡Vision Eye Institute, Queensland, Australia.

PURPOSE: To evaluate the safety and efficacy of a strictly applied inject and extend protocol for ranibizumab treatment of age-related macular degeneration.

METHODS: This is a prospective, multicenter, nonrandomized trial. Patients underwent standard induction with 3 intravitreal doses of 0.5 mg ranibizumab, each 1 month apart. Following this induction, patients were evaluated and received an injection at each visit. If they did not meet set criteria for signs of exudative disease the interval to the next visit was extended by 2 weeks and if exudative disease was present the interval was shortened by 2 weeks.

RESULTS: Vision improved by 1.3 lines ($P = 0.008$); 26% gained ≥ 3 lines of vision, 74% lost no lines of vision, and 95% avoided loss of ≥ 3 lines of vision.

CONCLUSION: This study shows that the Inject and Extend protocol is safe and efficacious for the treatment of age-related macular degeneration. Head-to-head studies are needed to compare directly with other regimens currently in use, as well as economic analysis to investigate the financial implications.

PMID: 23538578 [PubMed - as supplied by publisher]

J Ophthalmol. 2013;2013:268438. doi: 10.1155/2013/268438. Epub 2013 Feb 21.

Visual performance in patients with neovascular age-related macular degeneration undergoing treatment with intravitreal ranibizumab.

Sabour-Pickett S, Loughman J, Nolan JM, Stack J, Pesudovs K, Meagher KA, Beatty S.

Department of Optometry, School of Physics, Dublin Institute of Technology, Dublin, Ireland ; Institute of Eye Surgery and Institute of Vision Research, Whitfield Clinic, Waterford, Ireland; Macular Pigment Research Group, Waterford Institute of Technology, Waterford, Ireland.

Purpose: To assess visual function and its response to serial intravitreal ranibizumab (Lucentis, Genentech) in patients with neovascular age-related macular degeneration (nv-AMD).

Methods: Forty-seven eyes of 47 patients with nv-AMD, and corrected distance visual acuity (CDVA) logMAR 0.7 or better, undergoing intravitreal injections of ranibizumab, were enrolled into this prospective study. Visual function was assessed using a range of psychophysical tests, while mean foveal thickness (MFT) was determined by optical coherence tomography (OCT).

Results: Group mean ($\pm$ sd) MFT reduced significantly from baseline (233 ($\pm$ 59)) to exit (205 ($\pm$ 40)) ($P = 0.001$). CDVA exhibited no change between baseline and exit visits ($P = 0.48$ and $P = 0.31$, resp.). Measures of visual function that did exhibit statistically significant improvements ($P < 0.05$ for all) included reading acuity, reading speed, mesopic and photopic contrast sensitivity (CS), mesopic and photopic glare disability (GD), and retinotopic ocular sensitivity (ROS) at all eccentricities.

Conclusion: Eyes with nv-AMD undergoing intravitreal ranibizumab injections exhibit improvements in many parameters of visual function. Outcome measures other than CDVA, such as CS, GD, and ROS, should not only be considered in the design of studies investigating nv-AMD, but also in treatment and retreatment strategies for patients with the condition.

PMID: 23533703 [PubMed] PMCID: PMC3595676

Eur J Ophthalmol. 2013 Mar 28;0. doi: 10.5301/ejo.5000248. [Epub ahead of print]

Effect of VEGF and anti-VEGF compounds on retinal pigment epithelium permeability: an in vitro study.

Campa C.

St Paul's Eye Unit, Royal Liverpool University Hospital, Liverpool - United Kingdom.

Objective: To evaluate the effect of 2 vascular endothelial growth factor (VEGF) isoforms (121 and 165) and 2 anti-VEGF compounds (ranibizumab and pegaptanib sodium) on the permeability of human retinal pigment epithelium (RPE) cells in vitro.

Methods: The RPE permeability was assessed on ARPE19 cells grown onto inserts of polytetrafluoroethylene previously treated with ammonia gas plasma. Paracellular permeability to ions was measured by mean of transepithelial electrical resistance (TEER). Permeability to non-ionic molecules was gathered by the amount of fluorescein dextran (FD) passing across the monolayer within 2 hours.

Results: Only VEGF165 applied at the apical side of the monolayer induced a statistically significant decrease of TEER ($p < 0.001$). No changes in TEER were observed when pegaptanib sodium or ranibizumab were apically administered together with VEGF165. Both VEGF isoforms significantly increased permeability to 4 kDa dextran ($p < 0.01$). Apical administration of ranibizumab or pegaptanib sodium as well as coadministration of pegaptanib sodium with VEGF121 or VEGF165 induced a statistically significant increase of permeability to 4 kDa FD.

Conclusion: Both VEGF isoforms and anti-VEGF compounds exert an effect on human RPE permeability in vitro.

PMID: 23539459 [PubMed - as supplied by publisher]

Drugs Aging. 2013 Mar 29. [Epub ahead of print]

Ranibizumab: A Review of Its Use in the Treatment of Neovascular Age-Related Macular Degeneration.

Frampton JE.

Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand, demail@springer.com.

Abstract: Ranibizumab (Lucentis®), an inhibitor of all vascular endothelial growth factor (VEGF) A isoforms, is approved for the intravitreal treatment of neovascular age-related macular degeneration (AMD). In pivotal trials, monthly injections of ranibizumab were superior to verteporfin photodynamic therapy in the treatment of predominantly classic choroidal neovascularization (CNV) due to neovascular AMD (ANCHOR) and sham in the treatment of minimally classic or occult CNV due to neovascular AMD (MARINA). Monthly or less frequent injections of ranibizumab are generally well tolerated and associated with low rates of ocular and systemic serious adverse events (SAEs). Less frequent dosing has been evaluated with the aim of reducing the burden, risk and cost of monthly injections. In the landmark CATT trial, monthly monitoring and retreatment as-needed with ranibizumab was equivalent to monthly treatment in terms of the vision gain at 1 year, but reduced the number of injections (and the related cost) by approximately one-half. In head-to-head comparisons, aflibercept administered bimonthly was noninferior to ranibizumab administered monthly (VIEW 1 and 2), bevacizumab administered monthly was equivalent to ranibizumab administered monthly (CATT), and bevacizumab administered as-needed was equivalent to ranibizumab administered as-needed (CATT). Bevacizumab is widely used (off-label) for economic reasons; while it was less costly than ranibizumab, it was associated with more systemic SAEs. Notwithstanding the availability of other similarly effective anti-VEGF therapies that are approved (aflibercept) or unapproved (bevacizumab), ranibizumab continues to set the standard as regards the totality of evidence from randomized clinical trials demonstrating its efficacy and tolerability (particularly that of the monthly regimen) in the treatment of neovascular AMD.

PMID: 23539234 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2013 Mar 26. pii: [iovs.13-11613v1](#). doi: [10.1167/iovs.13-11613](#). [Epub ahead of print]

Relationship Between the Second Reflective Band on Optical Coherence Tomography and Multifocal Electroretinography in Age-Related Macular Degeneration.

Wu Z, Ayton LN, Guymer RH, Luu CD.

Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, VIC, Australia.

Abstract

PURPOSE: The second hyper-reflective on spectral domain optical coherence tomography (SD-OCT) has been suggested to correlate with the photoreceptor inner segment ellipsoids (ISe). The purpose of this study was to determine the relationship between the intensity of the ISe band and retinal function measured by multifocal electroretinography (mfERG) in patients with early age-related macular degeneration (AMD).

METHODS: A high-resolution horizontal line-scan through the fovea on SD-OCT and a mfERG recording were performed in one eye of 29 early AMD and 31 control participants. The relative intensity of the ISe band within 1000µm of the fovea was quantified using ImageJ (software). The relationships between the relative intensity of the ISe band and the mfERG response parameters (P1 amplitude and implicit time) within the three central hexagons along the horizontal axis were determined.

RESULTS: In normal participants, the relative intensity of the ISe band was significantly correlated with age ($r = -0.634$, $p < 0.001$) and also exhibited a topographic variation. On average, the relative intensity of the

ISe band was significantly lower in patients with early AMD (1.77 ± 0.26) compared to control subjects (1.95 ± 0.27 , $p < 0.001$) of a similar age range. The relative intensity of the ISe band was significantly correlated with the mfERG P1 implicit time ($r = -0.745$, $p < 0.001$), but not P1 amplitude ($r = 0.144$, $p = 0.281$).

CONCLUSIONS: The relative intensity of the ISe band reduced with age and further in early AMD. The relative intensity was significantly correlated with mfERG P1 implicit time.

PMID: 23532524 [PubMed - as supplied by publisher]

Retina. 2013 Mar 27. [Epub ahead of print]

SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY ANALYSIS OF MACULAR CHANGES IN TILTED DISK SYNDROME.

Cohen SY, Dubois L, Nghiem-Buffer S, Fajnkuchen F, Delahaye-Mazza C, Quentel G, Gaudric A, Tadayoni R.

*Ophthalmology Center for Imaging and Laser, Paris, France †Department of Ophthalmology, Lariboisière Hospital, University Paris Diderot, Sorbonne Paris Cité-APHP, Paris, France.

PURPOSE: To evaluate the prevalence of macular complications in tilted disk syndrome by spectral domain optical coherence tomography (OCT).

METHODS: A monocentric retrospective study of consecutive patients with tilted disk syndrome, whose eyes were examined by spectral domain OCT (Cirrus; Zeiss) and fundus photography.

RESULTS: Fifty consecutive patients (39 women and 11 men; age range, 41-96 years) with uni- or bilateral tilted disk syndrome were enrolled. All affected eyes ($n = 92$) were imaged by spectral domain OCT and fundus photography. Fluorescein and/or indocyanine green angiography were performed in 33 patients (66%). Macular anomalies or complications were observed in 71 eyes (77.1%). Specifically, retinal pigment epithelial changes were described in 34 eyes (36.9%), choroidal neovascularization in 24 eyes (26%), and macular serous retinal detachment in 16 eyes (17.3%). Epiretinal membrane in 9 eyes (9.7%), myopic foveoschisis in 5 eyes (5.4%), and lamellar macular hole in 3 eyes (3.2%) were also detected relatively frequently by spectral domain OCT. Surprisingly, fovea plana was observed in 5 eyes (5.4%). Eleven eyes, complicated by choroidal neovascularization, were treated with ranibizumab, with a mean visual gain of 7.9 letters on Early Treatment Diabetic Retinopathy Study chart.

CONCLUSION: Tilted disk syndrome can be associated with potentially severe macular complications. Spectral domain OCT allowed the recognition of additional macular changes associated with tilted disk syndrome, such as epiretinal membranes, myopic foveoschisis, and fovea plana.

PMID: 23538581 [PubMed - as supplied by publisher]

Optom Vis Sci. 2013 Mar 22. [Epub ahead of print]

Handwriting with a Preferred Retinal Locus for AMD with Scotomas.

Timberlake GT, Bothwell RJ, Moyer K.

*PhD †MS, CCRP ‡OD, FAAO Kansas City Veterans Administration Medical Center, Kansas City, Missouri.

PURPOSE: Individuals with macular scotomas from age-related macular degeneration frequently have difficulty writing legibly. The purpose of this study was to investigate the causes of this difficulty by documenting the location of the retinal image of the pen used for writing in relation to the scotoma and

fixational preferred retinal locus (fPRL).

METHODS: Subjects with macular scotomas from age-related macular degeneration and visually normal age-matched controls wrote words while observing their hand, pen, and text in a scanning laser ophthalmoscope. Scanning laser ophthalmoscope video images were analyzed to find the retinal positions of the subject's scotoma, fixation area, and pen tip.

RESULTS: Control subjects placed their fovea and scotoma subjects placed their fPRL on or very close to the pen tip for both cursive writing and printing. Scotoma subjects' written text sloped downward at a greater angle than controls'. Text angle was negatively correlated with fPRL eccentricity, visual acuity, and the amount the scotoma obscured the writing guides. When printing, control subjects placed their fovea precisely in the center of printing box guides, whereas scotoma subjects exhibited highly dispersed placement of the fPRL.

CONCLUSIONS: The principal finding is that, because the retinal locations of the pen tip and the fPRL or fovea are coincident or very close, the fPRL and fovea are "monitoring" the pen tip and its location on the page. It is the PRL determined by asking subjects to fixate (i.e., the fPRL) that is used when handwriting, not a separate "handwriting" PRL. The poor handwriting performance of those with macular scotomas seems to be primarily caused by difficulty in placing letters in the appropriate location probably because of reduced visual acuity of the fPRL and scotoma obscuration of the area on which to write.

PMID: 23528451 [PubMed - as supplied by publisher]

Retina. 2013 Mar 27. [Epub ahead of print]

SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY-DETERMINED MORPHOLOGIC PREDICTORS OF AGE-RELATED MACULAR DEGENERATION-ASSOCIATED GEOGRAPHIC ATROPHY PROGRESSION.

Moussa K, Lee JY, Stinnett SS, Jaffe GJ.

*Department of Ophthalmology, Duke University Medical Center, Durham, North Carolina; and

†Department of Ophthalmology, Asan Medical Center, University of Ulsan, Seoul, Korea.

PURPOSE: To correlate spectral domain optical coherence tomography (SD OCT)-determined morphologic alterations in eyes with geographic atrophy because of age-related macular degeneration with lesion size, enlargement rate, and the presence of multifocal patches of atrophy.

METHODS: Forty-three eyes of 43 patients with age-related macular degeneration-associated geographic atrophy were visualized by SD OCT and fundus autofluorescence imaging. The baseline area of geographic atrophy and enlargement rates over at least 24 weeks were calculated from the fundus autofluorescence images. The mean and median follow-up times were 47.4 and 48 weeks, respectively. Morphologic alterations were evaluated in the baseline SD OCT images. Ninety-seven SD OCT scans per eye were graded and included in the analysis. Correlations between morphologic alterations and the rate of lesion enlargement, size, and focality, and the diffuse trickling fundus autofluorescence pattern were determined.

RESULTS: The mean and median enlargement rates were 2.07 mm/year (n = 43; SD, 1.30) and 2.02 mm/year, respectively. Outer retinal tubulations (P = 0.003) and irregular elevations of the retinal pigment epithelium/Bruch membrane complex (P < 0.001) in the atrophic region, and splitting of the retinal pigment epithelium/Bruch membrane complex at 2 junctional zone borders (P = 0.02) correlated with faster enlargement. Outer retinal tubulations (P = 0.096), irregular elevations of the retinal pigment epithelium/Bruch membrane complex (P = 0.010), and crown-like elevations with debris beneath in the atrophic region (P = 0.063) correlated with larger lesion size. Hyperreflective plaques in the outer retina appeared more frequently in eyes with multifocal patches of atrophy (P = 0.005).

CONCLUSION: Distinct morphologic alterations visible on SD OCT imaging in eyes with geographic atrophy because of age-related macular degeneration are associated with faster enlargement rates, larger lesion size, and multifocal patches of atrophy.

PMID: 23538573 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Mar 28. pii: iovs.12-11521v1. doi: 10.1167/iov.12-11521. [Epub ahead of print]

Comparative Analysis of Repeatability of Manual and Automated Choroidal Thickness Measurements in Non-Neovascular Age-Related Macular Degeneration.

Lee S, Fallah N, Forooghian F, Ko A, Pakzad-Vaezi K, Merkur AB, Kirker AW, Albiani DA, Young M, Sarunic MV, Beg MF.

School of Engineering Science, Simon Fraser University, 8888 University Drive, Burnaby, BC, V5A 1S6, Canada.

PURPOSE: To compare the reproducibility and mutual agreement of the subfoveal choroidal thickness measurements by expert raters and an automated algorithm in enhanced depth imaging optical coherence tomography (EDI-OCT) images of eyes with non-neovascular age-related macular degeneration (AMD).

METHODS: Forty-four patients with non-neovascular AMD were recruited and EDI-OCT images were acquired. Subfoveal choroidal thickness was measured manually by two expert raters and automatically by a graph-cut based algorithm. Drusen area was measured using the automated software (version 6) of Cirrus SD-OCT. The manual and automated choroidal thickness measurements were compared in reproducibility, mutual agreement, and correlation with drusen area.

RESULTS: The mean subfoveal choroidal thickness was $246 \pm 63 \mu\text{m}$ for the first rater, 214 ± 68 for the second rater, and 209 ± 53 for the automated algorithm. Intraclass correlation coefficients (ICC) and 95 % confidence intervals (CI) were 0.96 (CI: 0.94-0.98) between the raters, 0.85 (CI: 0.77-0.90) between the first rater and the automated algorithm, and 0.84 (CI: 0.75-0.89) between the second rater and the automated algorithm. Repeat scan measurement ICCs were 0.91 (CI: 0.86-0.94) for the first rater, 0.96 (CI: 0.94-0.97) for the second rater, and 0.87 (CI: 0.80-0.92) for the automated algorithm. Both manual and automated measurements were correlated with drusen area.

CONCLUSION: The automated algorithm yielded generally yielded smaller choroidal thickness than the raters with a moderate level of agreement. However its repeat scan measurement repeatability was comparable to that of the manual measurements. The mean difference between the raters indicated possible biases in different raters and rating sessions. The correlation of the automated measurements with the drusen area was comparable to that of the manual measurements. Automated subfoveal choroidal thickness measurement has potential use in clinical practice and clinical trials with possibility for reduced time and labor cost.

PMID: 23538060 [PubMed - as supplied by publisher]

Pathogenesis

Retina. 2013 Mar 27. [Epub ahead of print]

ASSOCIATION OF PARAOXONASE 1 L55M AND Q192R SINGLE-NUCLEOTIDE POLYMORPHISMS WITH AGE-RELATED MACULAR DEGENERATION.

Söğüt E, Ortak H, Aydoğan L, Benli I.

Departments of *Biochemistry, and †Ophthalmology, Faculty of Medicine, Gaziosmanpaşa University, Tokat, Turkey.

PURPOSE: To determine if paraoxonase 1 (PON1) gene polymorphisms have an effect on the risk of having age-related macular degeneration (AMD).

METHODS: The study population consisted of 142 patients who were diagnosed with either exudative or atrophic AMD and 138 sex- and age-matched controls without AMD. Genotyping of the PON1 L55M and Q192R single-nucleotide polymorphisms was performed using real-time polymerase chain reaction and commercially produced kits. A full ophthalmic evaluation was performed in each subject, and all subjects were screened for hypertension, diabetes, hypercholesterolemia, and smoking history.

RESULTS: The PON1 MM and QQ genotypes were less frequent in patients with AMD than in control subjects (MM: 4 vs. 13%, $P = 0.015$; QQ: 15 vs. 27%, $P = 0.020$). A multivariate logistic regression analysis was also conducted. After adjusting for age, gender, and the prevalence of smoking, hypertension, diabetes, and hypercholesterolemia, the MM and QQ genotypes (MM/ QQ vs. LL + LM/QR + RR) were found to be associated with a decreased risk of AMD (MM: odds ratio = 0.24, $P = 0.007$, 95% confidence interval: 0.09-0.68; QQ: odds ratio = 0.46, $P = 0.013$, 95% confidence interval: 0.25-0.85).

CONCLUSION: The authors found that subjects with the PON1 MM and QQ genotypes had a lower risk of AMD.

PMID: 23538572 [PubMed - as supplied by publisher]

Int J Mol Med. 2013 Mar 20. doi: 10.3892/ijmm.2013.1310. [Epub ahead of print]

Amyloid- β -induced matrix metalloproteinase-9 secretion is associated with retinal pigment epithelial barrier disruption.

Cao L, Wang H, Wang F.

Department of Ophthalmology, Shanghai Tenth People's Hospital affiliated with Tongji University, School of Medicine, Shanghai, P.R. China.

Abstract: Local and chronic inflammation induced by amyloid- β (A β) plays a central role in the development of age-related macular degeneration. The retina is an immune-privileged site due to local tissue barrier. Yet, the manner by which immune cells pass through this barrier and accumulate in the retina remains unclear. Matrix metalloproteinases (MMPs) induce barrier disruption via proteolysis of epithelial tight junction (TJ) proteins. We hypothesized that A β -induced MMP secretion causes disruption of epithelial barrier integrity. To test this hypothesis, human adult retinal pigment epithelial (haRPE) cells were exposed to A β , and the expression of MMP-2 and MMP-9 was detected using gelatin zymography. To demonstrate the key role of MMPs in modulating epithelial barrier structure, the MMP agonist 4-aminophenylmercuric acetate (APMA), an MMP inhibitor (GM6001) and siRNA against MMP-9 were employed for comparison. We found that MMP-9, secreted by A β - or APMA-stimulated cells, mediated low transepithelial electrical resistance (TER) and high transepithelial permeability by disrupting TJ proteins. However, these alterations were reduced by the MMP inhibitor GM6001 or by silencing of the MMP-9 gene. Our findings suggest that the degradation of TJ proteins such as zonula occludens-1, occludin and F-actin by MMP-9 secreted by A β -stimulated cells constitutes an important mechanism in the breakdown of the barrier which contributes to chronic inflammation in the retina of age-related macular degeneration.

PMID: 23525277 [PubMed - as supplied by publisher]

Aging Cell. 2013 Mar 22. doi: 10.1111/accel.12072. [Epub ahead of print]

Balance between autophagic pathways preserves retinal homeostasis.

Rodríguez-Muela N, Koga H, García-Ledo L, de la Villa P, de la Rosa EJ, Cuervo AM, Boya P.

Department of Cellular and Molecular Biology, CIB, CSIC, Ramiro de Maeztu 9, E-28040, Madrid, Spain.

Abstract: Aging contributes to the appearance of several retinopathies and is the largest risk factor for aged-related macular degeneration, major cause of blindness in the elderly population. Accumulation of undegraded material as lipofuscin represents a hallmark in many pathologies of the aged eye. Autophagy is a highly conserved intracellular degradative pathway that plays a critical role in the removal of damaged cell components to maintain the cellular homeostasis. A decrease in autophagic activity with age observed in many tissues has been proposed to contribute to the aggravation of age-related diseases. However, the participation of different autophagic pathways to the retina physiopathology remains unknown. Here we describe a marked reduction in macroautophagic activity in the retina with age, which coincides with an increase in chaperone-mediated autophagy (CMA). This increase in CMA is also observed during retinal neurodegeneration in the *Atg5^{flox/flox}*; *nestin-Cre* mice, a mouse model with downregulation of macroautophagy in neuronal precursors. In contrast to other cell types, this autophagic cross-talk in retinal cells is not bi-directional and CMA inhibition renders cone photoreceptor very sensitive to stress. Temporal and cell-type specific differences in the balance between autophagic pathways may be responsible for the specific pattern of visual loss that occurs with aging. Our results show for the first time a cross-talk of different lysosomal proteolytic systems in the retina during normal aging and may help the development of new therapeutic intervention for age-dependent retinal diseases.

PMID: 23521856 [PubMed - as supplied by publisher]

Int J Inflam. 2013;2013:503725. doi: 10.1155/2013/503725. Epub 2013 Mar 7.

Infiltration of proinflammatory m1 macrophages into the outer retina precedes damage in a mouse model of age-related macular degeneration.

Cruz-Guilloty F, Saeed AM, Echegaray JJ, Duffort S, Ballmick A, Tan Y, Betancourt M, Viteri E, Ramkellawan GC, Ewald E, Feuer W, Huang D, Wen R, Hong L, Wang H, Laird JM, Sene A, Apte RS, Salomon RG, Hollyfield JG, Perez VL.

Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL 33136, USA ; Department of Microbiology and Immunology, University of Miami Miller School of Medicine, Miami, FL 33136, USA.

Abstract: Age-related macular degeneration (AMD) is a major cause of blindness in the developed world. Oxidative stress and inflammation are implicated in AMD, but precise mechanisms remain poorly defined. Carboxyethylpyrrole (CEP) is an AMD-associated lipid peroxidation product. We previously demonstrated that mice immunized with CEP-modified albumin developed AMD-like degenerative changes in the outer retina. Here, we examined the kinetics of lesion development in immunized mice and the presence of macrophages within the interphotoreceptor matrix (IPM), between the retinal pigment epithelium and photoreceptor outer segments. We observed a significant and time-dependent increase in the number of macrophages in immunized mice relative to young age-matched controls prior to overt pathology. These changes were more pronounced in BALB/c mice than in C57BL/6 mice. Importantly, IPM-infiltrating macrophages were polarized toward the M1 phenotype but only in immunized mice. Moreover, when *Ccr2*-deficient mice were immunized, macrophages were not present in the IPM and no retinal lesions were observed, suggesting a deleterious role for these cells in our model. This work provides mechanistic evidence linking immune responses against oxidative damage with the presence of proinflammatory macrophages at sites of future AMD and experimentally demonstrates that manipulating immunity may be a target for modulating the development of AMD.

PMID: 23533946 [PubMed] PMCID: PMC3606733

Philos Trans R Soc Lond B Biol Sci. 2013 Mar 25;368(1617):20120104. doi: 10.1098/rstb.2012.0104. Print 2013.

Self-assembly of protein aggregates in ageing disorders: the lens and cataract model.

Clark JI.

Departments of Biological Structure and Ophthalmology, University of Washington, , Seattle, WA 98195, USA.

Abstract: Cataract, neurodegenerative disease, macular degeneration and pathologies of ageing are often characterized by the slow progressive destabilization of proteins and their self-assembly to amyloid-like fibrils and aggregates. During normal cell differentiation, protein self-assembly is well established as a dynamic mechanism for cytoskeletal organization. With the increased emphasis on ageing disorders, there is renewed interest in small-molecule regulators of protein self-assembly. Synthetic peptides, mini-chaperones, aptamers, ATP and pantethine reportedly regulate self-assembly mechanisms involving small stress proteins, represented by human α B-crystallin, and their targets. Small molecules are being considered for direct application as molecular therapeutics to protect against amyloid and protein aggregation disorders in ageing cells and tissues in vivo. The identification of specific interactive peptide sites for effective regulation of protein self-assembly is underway using conventional and innovative technologies. The quantification of the functional interactions between small stress proteins and their targets in vivo remains a top research priority. The quantitative parameters controlling protein-protein interactions in vivo need characterization to understand the fundamental biology of self-assembling systems in normal cells and disorders of ageing.

PMID: 23530262 [PubMed - in process]

Ophthalmic Genet. 2013 Mar 28. [Epub ahead of print]

The Role of MMP2 (-1306C>T) and TIMP2 (-418 G>C) Promoter Variants in Age-related Macular Degeneration.

Ortak H, Demir S, Ateş O, Benli I, Söğüt E, Sahin M.

Department of Ophthalmology .

Abstract Purpose: To investigate the possible association between the matrix metalloproteinase 2 (-1306C>T) (rs 243865) and tissue inhibitors of matrix metalloproteinase 2 (-418 G>C) (rs 8179090) polymorphisms and the risk of age-related macular degeneration.

Methods: This case-controlled prospective study included 144 age-related macular degeneration patients and 172 control subjects. All subjects were screened for age, gender, hypertension (HT), diabetes (DM), and body mass index (BMI). Serum levels of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), total cholesterol (TC), and smoking were also determined. Genomic DNA was extracted from peripheral leukocytes from ethylenediaminetetraacetic acid anticoagulated blood. Genotyping of the MMP2 (-1306C>T) and TIMP2 (-418 G>C) polymorphisms was performed using real-time polymerase chain reaction.

Results: Genotype distributions or allelic frequencies of MMP2 (-1306C>T) and TIMP2 (-418 G>C) did not significantly differ between patients with AMD and control subjects. Similarly, no significant differences in either genotype distributions or allelic frequencies of MMP2 (-1306C>T) and TIMP2 (-418 G>C) were found between dry and wet AMD.

Conclusion: MMP2 (-1306C>T) and TIMP2 (-418 G>C) promoter variants are unlikely to have a major role in age-related macular degeneration risk susceptibility.

PMID: 23536957 [PubMed - as supplied by publisher]

Epidemiology

JAMA. 2013 Mar 27;309(12):1227-8. doi: 10.1001/jama.2013.2041.

Aspirin use and risk of macular degeneration--reply.

Klein BE, Howard KP.

Comment on Long-term use of aspirin and age-related macular degeneration. [JAMA. 2012]

PMID: 23532232 [PubMed - indexed for MEDLINE]

JAMA. 2013 Mar 27;309(12):1227. doi: 10.1001/jama.2013.2035.

Aspirin use and risk of macular degeneration.

Hu X, Tang S.

Comment on Aspirin use and risk of macular degeneration--reply. [JAMA. 2013]

PMID: 23532231 [PubMed - indexed for MEDLINE]

JAMA. 2013 Mar 27;309(12):1226. doi: 10.1001/jama.2013.2038.

Aspirin use and risk of macular degeneration.

Nowroozzadeh MH.

Comment on Aspirin use and risk of macular degeneration--reply. [JAMA. 2013]

PMID: 23532230 [PubMed - indexed for MEDLINE]

BMC Ophthalmol. 2013 Mar 28;13(1):9. [Epub ahead of print]

Prevalence and pattern of vitreo-retinal diseases in Nepal: the Bhaktapur Glaucoma Study.

Thapa SS, Thapa R, Paudyal I, Khanal S, Aujla J, Paudyal G, Rens G.

BACKGROUND: Vitreo-retinal diseases are among the leading causes of visual impairment and blindness worldwide. This study reports the prevalence and pattern of vitreo-retinal diseases in the Bhaktapur Glaucoma Study (BGS), a population based study conducted in Nepal.

METHODS: BGS was a population based cross-sectional study involving 4800 subjects aged 40 years and over from Bhaktapur district. Subjects were selected using a cluster sampling methodology and a door-to-door enumeration. All subjects underwent a detailed ocular examination at the base hospital which included log MAR visual acuity, refraction, applanation tonometry and a dilated fundus examination. Fundus photography, optical coherence tomography and fundus fluorescein angiography were performed where indicated.

RESULTS: Complete data was available for 3966 (82.62%) out of the total of 4800 enumerated subjects. The mean age was 55.08 years (SD 11.51). The overall prevalence of vitreo-retinal disorders was 5.35% (95% CI, 4.67 - 6.09). Increasing age was associated with a higher prevalence of vitreo-retinal disorders ($P < 0.001$). The prevalence of diabetes mellitus was 7.69% (95% CI, 6.88 - 8.56). Age-related macular degeneration (AMD) was the most common vitreo-retinal disorder with a prevalence of 1.50% (95% CI, 1.15 - 1.94), increasing significantly with age. The prevalence of diabetic retinopathy among the study population was 0.78% (95% CI, 0.53 - 1.11) and among the diabetic population 10.16% (95% CI, 7.01 -

14.12). The population prevalence of other retinal disorders were hypertensive retinopathy 0.88%, macular scar 0.37%, retinal vein occlusion 0.50%, macular hole 0.20%, retinitis pigmentosa 0.12%. and retinal detachment 0.10%. The prevalence of low vision and blindness due to vitreo-retinal disorders was 1.53% (95% CI, 1.18 - 1.97) and 0.65% (95% CI, 0.43 - 0.96), respectively. The prevalence of low vision and blindness was 28.77% (95% CI, 22.78-35.37) and 12.26% (95% CI, 8.17-17.45), respectively among cases with vitreo-retinal disorders. Blindness was observed to be unilateral in 19 cases (73%), and bilateral in 7 cases (27%).

CONCLUSIONS: The prevalence of vitreo-retinal disorders in this Nepalese population was 5.35%, which increased significantly with age. AMD was the predominant retinal condition followed by diabetic retinopathy. One fourth of the subjects with vitreo-retinal disorder had low vision. Taking into consideration the aging population and emerging systemic diseases such as diabetes mellitus and hypertension, vitreo-retinal disorders could be of future public health importance.

PMID: 23537395 [PubMed - as supplied by publisher]

Med Lav. 2013 Jan-Feb;104(1):3-23.

[Occupational diseases caused by artificial optical radiations (AOR)]. [Article in Italian]

Taino G, Paraluppi P, Giorgi M, D'Orso MI, Piccoli B.

Unità Operativa Ospedaliera di Medicina del Lavoro, IRCCS Fondazione S. Maugeri, Pavia.
giuseppe.taino@fsm.it

BACKGROUND: Italian national legislation guarantees safety and health for workers exposed to artificial optical radiations (AOR) by Legislative Decree 81/2008.

OBJECTIVES AND METHODS: Effects and damages to health resulting from AOR exposure were analyzed from literature data.

RESULTS: Ultraviolet radiations (UV), particularly those in the wavelength range between 220 and 310 nm, causes chronic conjunctivitis and kerato-conjunctivitis. Skin cancer caused by UV exposure included basal cell carcinoma, squamous cell carcinoma and melanoma. As regards Infrared Radiations (portion of the spectrum between 780 nm and 1 mm), the biological effect is essentially of thermal nature. Exposure to blue light (portion of the spectrum of visible light radiation in a wavelength range between 380 and 550 nm) causes exclusively retinal damage and is considered to be responsible for the development of situations of age-related macular degeneration (AMD). Even if experimental data are available, at the present time there is still no epidemiological evidence of retinal damage caused by blue light.

CONCLUSIONS: The forensic criteria for investigating the causality link between occupational exposure to AOR and damage, and the methodology necessary for the assessment process, are reported. Two lists of occupational diseases which were included in the Italian Ministerial Decrees, issued respectively on April 2008 and 11 December 2009, are also considered. Lastly, on the basis of the current existing guidelines and scientific evidence, the authors propose occupational health surveillance protocols for workers exposed to AOR risk.

PMID: 23520883 [PubMed - in process]

Genetics

PLoS One. 2013;8(3):e58657. doi: 10.1371/journal.pone.0058657. Epub 2013 Mar 11.

A genome-wide association study for primary open angle glaucoma and macular degeneration reveals novel Loci.

Macular Disease Foundation Australia Suite 902, 447 Kent Street, Sydney, NSW, 2000, Australia.

Tel: +61 2 9261 8900 | Fax: +61 2 9261 8912 | E: research@mdfoundation.com.au | W: www.mdfoundation.com.au

Scheetz TE, Fingert JH, Wang K, Kuehn MH, Knudtson KL, Alward WL, Boldt HC, Russell SR, Folk JC, Casavant TL, Braun TA, Clark AF, Stone EM, Sheffield VC.

Department of Ophthalmology and Visual Sciences, The University of Iowa, Iowa City, Iowa, United States of America ; Department of Biomedical Engineering, The University of Iowa, Iowa City, Iowa, United States of America ; Center for Bioinformatics and Computational Biology, The University of Iowa, Iowa City, Iowa, United States of America.

Abstract: Glaucoma and age-related macular degeneration (AMD) are the two leading causes of visual loss in the United States. We utilized a novel study design to perform a genome-wide association for both primary open angle glaucoma (POAG) and AMD. This study design utilized a two-stage process for hypothesis generation and validation, in which each disease cohort was utilized as a control for the other. A total of 400 POAG patients and 400 AMD patients were ascertained and genotyped at 500,000 loci. This study identified a novel association of complement component 7 (C7) to POAG. Additionally, an association of central corneal thickness, a known risk factor for POAG, was found to be associated with ribophorin II (RPN2). Linked monogenic loci for POAG and AMD were also evaluated for evidence of association, none of which were found to be significantly associated. However, several yielded putative associations requiring validation. Our data suggest that POAG is more genetically complex than AMD, with no common risk alleles of large effect.

PMID: 23536807 [PubMed - in process]

Ophthalmology. 2013 Mar 20. pii: S0161-6420(13)00140-1. doi: 10.1016/j.ophtha.2013.02.007. [Epub ahead of print]

Inclusion of Genotype with Fundus Phenotype Improves Accuracy of Predicting Choroidal Neovascularization and Geographic Atrophy.

Perlee LT, Bansal AT, Gehrs K, Heier JS, Csaky K, Allikmets R, Oeth P, Paladino T, Farkas DH, Rawlings PL, Hageman GS.

Sequenom, Inc, San Diego, California. Electronic address: lperlee@sequenom.com.

PURPOSE: The accuracy of predicting conversion from early-stage age-related macular degeneration (AMD) to the advanced stages of choroidal neovascularization (CNV) or geographic atrophy (GA) was evaluated to determine whether inclusion of clinically relevant genetic markers improved accuracy beyond prediction using phenotypic risk factors alone.

DESIGN: Cohort study.

PARTICIPANTS: White, non-Hispanic subjects participating in the Age-Related Eye Disease Study (AREDS) sponsored by the National Eye Institute consented to provide a genetic specimen. Of 2415 DNA specimens available, 940 were from disease-free subjects and 1475 were from subjects with early or intermediate AMD.

METHODS: DNA specimens from study subjects were genotyped for 14 single nucleotide polymorphisms (SNPs) in genes shown previously to associate with CNV: ARMS2, CFH, C3, C2, FB, CFHR4, CFHR5, and F13B. Clinical demographics and established disease associations, including age, sex, smoking status, body mass index (BMI), AREDS treatment category, and educational level, were evaluated. Four multivariate logistic models (phenotype; genotype; phenotype + genotype; and phenotype + genotype + demographic + environmental factors) were tested using 2 end points (CNV, GA). Models were fitted using Cox proportional hazards regression to use time-to-disease onset data.

MAIN OUTCOME MEASURES: Brier score (measure of accuracy) was used to identify the model with the lowest prediction error in the training set. The most accurate model was subjected to independent statistical validation, and final model performance was described using area under the receiver operator curve (AUC)

or C-statistic.

RESULTS: The CNV prediction models that combined genotype with phenotype with or without age and smoking revealed superior performance (C-statistic = 0.96) compared with the phenotype model based on the simplified severity scale and the presence of CNV in the nonstudy eye (C-statistic = 0.89; $P < 0.01$). For GA, the model that combined genotype with phenotype demonstrated the highest performance (AUC = 0.94). Smoking status and ARMS2 genotype had less of an impact on the prediction of GA compared with CNV.

CONCLUSIONS: Inclusion of genotype assessment improves CNV prediction beyond that achievable with phenotype alone and may improve patient management. Separate assessments should be used to predict progression to CNV and GA because genetic markers and smoking status do not equally predict both end points.

FINANCIAL DISCLOSURE(S):

PMID: 23523162 [PubMed - as supplied by publisher]

Ophthalmic Genet. 2013 Mar 27. [Epub ahead of print]

CFH (rs1410996), HTRA1 (rs112000638) and ARMS2 (rs10490923) Gene Polymorphisms are Associated with AMD Risk in Spanish Patients.

Cruz-González F, Cieza-Borrella C, López Valverde G, Lorenzo-Pérez R, Hernández-Galilea E, González-Sarmiento R.

Departamento de Oftalmología, Hospital Universitario de Salamanca .

ABSTRACT Purpose: Age-related macular degeneration (AMD) is the main cause of legal blindness in the western adult population. We investigated the association between SNPs located in CFH, ARMS2 and HTRA1 and AMD in Spanish patients.

Patients and Methods: We obtained peripheral blood samples from 121 patients with a diagnosis of AMD (84 exudative and 37 atrophic) at the Department of Ophthalmology of the University Hospital of Salamanca. We took 91 subjects as a control group. We studied a single nucleotide polymorphism (SNP) in each patient for each of the genes associated with high susceptibility to developing AMD using Real-time PCR with TaqMan probes for CFH and ARMS2 polymorphisms and PCR-RFLP for HTRA1 polymorphism.

Results: We observed a statistically significant difference between patients and controls in the distribution of CFH rs1410996 genotypes, patients homozygous for the C-allele have twice the risk of developing the disease ($p = 0.010$; OR = 2,176 (1.194-3.964)). The analysis of ARMS2 rs10490923 polymorphism also showed differences in allelic distribution between the case and control groups ($p < 0.001$). Carriers of the T-allele appear more frequently in the group of patients ($p < 0.001$; OR = 3.340 (1.848-6.060)). Our results also confirm significant differences in the distribution of HTRA1 rs112000638 polymorphism with an increased representation of the G-allele in the patient's group ($p < 0.001$; OR = 6.254(3.463-12.280)). Our study also indicates that TTGG ARMS2/HTRA1 (rs10490923/rs112000638) haplotype increases the risk of developing AMD by 9 times.

Conclusions: Our results show that genotypes of ARMS2 (rs10490923), HTRA1 (rs112000638) and CFH (rs1410996) polymorphisms are related to an increased risk of suffering AMD in Spanish patients.

PMID: 23534868 [PubMed - as supplied by publisher]

Disclaimer: This newsletter is provided as a free service to eye care professionals by the Macular Disease Foundation Australia. The Macular Disease Foundation cannot be liable for any error or omission in this publication and makes no warranty of any kind, either expressed or implied in relation to this publication.