Drug treatment

Retina. 2017 Jul 4. [Epub ahead of print]

MACULAR ATROPHY AND MACULAR MORPHOLOGY IN AFLIBERCEPT-TREATED NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.


PURPOSE: To investigate the incidence and predictors of macular atrophy during treatment with aflibercept for neovascular age-related macular degeneration in Japanese patients.

METHODS: This study included patients with treatment-naive subfoveal neovascular age-related macular degeneration treated from December 2012 through January 2015. Patients were treated with bi-monthly aflibercept injections after 3 monthly loading injections for the first year. Diagnosis of retinal pigment epithelial atrophy was made based on color fundus photography, spectral-domain optical coherence tomography, and fundus autofluorescence. Baseline characteristics and morphological features were analyzed for their association with the development of macular atrophy.

RESULTS: This study included 123 eyes that had no baseline macular atrophy and treated with aflibercept injections for 12 months. Thirteen eyes (10.6%) developed new macular atrophy at 12 months. Logistic regression analysis showed that the presence of intraretinal fluid and thinner subfoveal choroidal thickness at baseline were associated with the development of macular atrophy after aflibercept treatment.

CONCLUSION: Macular atrophy developed in about 10% of eyes with neovascular age-related macular degeneration during 12 months of treatment with a fixed regimen of aflibercept. Intraretinal fluid and subfoveal choroidal thickness seem to be predictors for development of macular atrophy after anti-vascular endothelial growth factor (VEGF) therapy.

PMID: 28691937


Retrospective Analysis of the Effect of Aflibercept Loading Dose on the Retinal Vessel Diameters in Patients with Treatment-Naive Neovascular AMD.

Tetikoğlu M, Kurt MM, Sağdik HM, Aktaş S, Yıldırım MA, Özcura F.

BACKGROUND: To evaluate the effects of intravitreal aflibercept (IVA) on retinal vessel diameters in patients with neovascular age-related macular degeneration (AMD).

DESIGN, SETTING, AND PARTICIPANTS: A retrospective study conducted at the Kutahya Dumlupinar
University Faculty of Medicine included fifteen eyes of fifteen patients with treatment naive neovascular AMD.

METHODS: All eyes received IVA injections once per month for 3 months; untreated contralateral eyes were used as controls. The central retinal artery equivalent (CRAE), central retinal vein equivalent (CRVE), and artery-vein ratio (AVR) values were measured using a computer-based program before the first IVA injection and 30 days after the first, second, and third injections. The main outcome measurements were the central macular thickness (CMT), best-corrected visual acuity (BCVA), choroidal thickness, CRAE, CRVE, and artery-vein ratio (AVR).

RESULT: Significant vasoconstriction of the retinal arterioles was observed in all eyes treated with IVA when compared to baseline (p = 0.009). However no significant differences were found for CRVE or AVR throughout study period in treated eyes. In the control group, all parameters measured during each visit were similar to baseline measurements (p > 0.05). The mean BCVA significantly improved at the end of the loading dose of IVA, when compared to baseline (p = 0.006). After the IVA injections, the mean CMT and choroidal thickness were significantly reduced at all visits, compared to baseline (p < 0.001).

CONCLUSIONS: The current study showed that IVA led to significant retinal arteriolar vasoconstriction and choroidal thinning, which may cause reduced retinal blood flow.

PMID: 28697703

Other treatment & diagnosis

Ophthalmologe. 2017 Jul 13. [Epub ahead of print]

[Fluorescein, indocyanine green and optical coherence tomography angiography in patients with native exudative age-related macular degeneration]. [Article in German]

Pauleikhoff LJB, Blobner K, Wehrmann K, Feucht N, Lohmann CP, Maier M.

INTRODUCTION: The newly developed optical coherence tomography angiography (OCT-A) has provided new means to depict the vascular plexus in neovascular age-related macular degeneration (nAMD). If these images are to be used as a basis for therapeutic decisions, it is of vital importance to classify choroidal neovascularization (CNV) as either classical or occult. This study aimed at comparing the findings in OCT-A imaging of CNV with the traditional multimodal imaging through fluorescein angiography (FLA) and indocyanine green angiography (ICGA).

METHODS: For this investigation 13 eyes from 13 patients with CNV on the basis of untreated nAMD were studied using FLA, ICGA, spectral domain OCT and OCT-A. All CNV were classified on the basis of SD-OCT and OCT-A images by two independent raters. Thereafter FLA and ICGA images were analyzed to set the gold standard for the classification and the ratings were compared to the previous SD-OCT and OCT-A results.

RESULTS: 88% of eyes were correctly classified as either classical or occult CNV on the basis of SD-OCT and OCT-A images. Based on the CNV subgroups, 93% of classical CNV were identified using OCT-A images. In contrast occult CNV was correctly classified in 83% of patients. The interrater agreement was 77%. In general it was noted that the more the retina was pathologically altered, e. g. by edema or vascular pigment epithelium detachment, the harder it became to correctly classify the CNV.

DISCUSSION: These results show that OCT-A can be used as an interesting addition in the diagnosis of CNV in nAMD. All CNV could be visualized using OCT-A and especially classical CNV could be clearly recognized in most cases. In contrast occult CNV could be identified in slightly fewer cases.

PMID: 28707091

Automated analysis of retinal imaging using machine learning techniques for computer vision.

De Fauw J, Keane P, Tomasev N, Visentin D, van den Driessche G, Johnson M, Hughes CO1, Chu C1, Ledsam J1, Back T1, Peto T2, Rees G3, Montgomery H4, Raine R5, Ronneberger O1, Cornebise J1.

Author information

Abstract

There are almost two million people in the United Kingdom living with sight loss, including around 360,000 people who are registered as blind or partially sighted. Sight threatening diseases, such as diabetic retinopathy and age related macular degeneration have contributed to the 40% increase in outpatient attendances in the last decade but are amenable to early detection and monitoring. With early and appropriate intervention, blindness may be prevented in many cases. Ophthalmic imaging provides a way to diagnose and objectively assess the progression of a number of pathologies including neovascular ("wet") age-related macular degeneration (wet AMD) and diabetic retinopathy. Two methods of imaging are commonly used: digital photographs of the fundus (the 'back' of the eye) and Optical Coherence Tomography (OCT, a modality that uses light waves in a similar way to how ultrasound uses sound waves). Changes in population demographics and expectations and the changing pattern of chronic diseases creates a rising demand for such imaging. Meanwhile, interrogation of such images is time consuming, costly, and prone to human error. The application of novel analysis methods may provide a solution to these challenges. This research will focus on applying novel machine learning algorithms to automatic analysis of both digital fundus photographs and OCT in Moorfields Eye Hospital NHS Foundation Trust patients. Through analysis of the images used in ophthalmology, along with relevant clinical and demographic information, DeepMind Health will investigate the feasibility of automated grading of digital fundus photographs and OCT and provide novel quantitative measures for specific disease features and for monitoring the therapeutic success.

PMID: 27830057 PMCID: PMC5082593.2


epiACO - a method for identifying epistasis based on ant Colony optimization algorithm.

Sun Y, Shang J, Liu JX, Li S, Zheng CH.

BACKGROUND: Identifying epistasis or epistatic interactions, which refer to nonlinear interaction effects of single nucleotide polymorphisms (SNPs), is essential to understand disease susceptibility and to detect genetic architectures underlying complex diseases. Though many works have been done for identifying epistatic interactions, due to their methodological and computational challenges, the algorithmic development is still ongoing.

RESULTS: In this study, a method epiACO is proposed to identify epistatic interactions, which based on ant colony optimization algorithm. Highlights of epiACO are the introduced fitness function Svalue, path selection strategies, and a memory based strategy. The Svalue leverages the advantages of both mutual information and Bayesian network to effectively and efficiently measure associations between SNP combinations and the phenotype. Two path selection strategies, i.e., probabilistic path selection strategy and stochastic path selection strategy, are provided to adaptively guide ant behaviors of exploration and exploitation. The memory based strategy is designed to retain candidate solutions found in the previous iterations, and compare them to solutions of the current iteration to generate new candidate solutions, yielding a more accurate way for identifying epistasis.

CONCLUSIONS: Experiments of epiACO and its comparison with other recent methods epiMODE, TEAM, BOOST, SNPRuler, AntEpiSeeker, AntMiner, MACOED, and IACO are performed on both simulation data...
sets and a real data set of age-related macular degeneration. Results show that epiACO is promising in identifying epistasis and might be an alternative to existing methods.

PMID: 28694848 PMCID: PMC5500974


Fundus autofluorescence: the key in the diagnosis of maternally inherited diabetes and deafness.
Esteban O, Mateo J, Peiro C, Del Buey MÁ, Ascaso FJ.
PMID: 28696040

Pathogenesis


Evaluation of MicroRNA Responses in ARPE-19 Cells Against The Oxidative Stress.
Ayaz L, Dinç E.

PURPOSE: This study aimed to determine microRNA (miRNA) expression profile of human retinal pigment epithelium cell (ARPE-19) against the oxidative stress induced by hydrogen peroxide (H2O2).

METHODS: ARPE-19 cells were incubated with different concentrations of H2O2 (200, 600 and 800 µM) for 18 hours, and then cell viability, vascular endothelial growth factor levels and total oxidant status were evaluated. Expressions of 1152 miRNA were determined by quantitative Real-Time PCR in each group.

RESULTS: Expressions of 90 miRNA were significantly changed in the ARPE-19 cells incubated with H2O2 compared to control group. However, miR-143-3p was only found to be expressed in groups incubated with H2O2. While 24 miRNA (hsa-miR-200c-3p, miR-192-5p, miR-194-5p, miR-141-3p, miR-658, miR-18b-5p, miR-486-5p, miR-525-3p, miR-493-3p, miR-518d-3p, miR-29b-1-5p, miR-675-3p, miR-1238-3p, miR-195-3p, miR-1539, miR-490-5p, miR-3200-5p, miR-1273d, miR-130a-5p, miR-30b-5p, miR-1247-5p, miR-1910-5p, miR27a-5p and miR-200b-3p) upregulated due to the increased dose of H2O2, 9 miRNA (hsa-miR-96-5p, miR-33a-5p, miR-345-5p, miR-106b-3p, miR-1285-3p, miR-23b-5p, miR-27b-5p, miR-103a-3p and miR-4289) were also found to be down-regulated.

CONCLUSION: This study suggests that oxidative stress may be an important factor on expression of miRNAs in ARPE-19 cells. These miRNAs may have a role in the pathogenesis of age-related macular degeneration related to oxidative stress. However, this relationship needs to be examined in new studies by evaluation of pathways and target genes.

PMID: 28707489


Protective effects of melatonin and memantine in human retinal pigment epithelium (ARPE-19) cells against 2-ethylpyridine-induced oxidative stress: Implications for age-related macular degeneration.
Bardak H, Uğuz AC, Bardak Y.

PURPOSE: To investigate the possible protective effects of melatonin and memantine (MMT) against 2-ethylpyridine (2-EP)-induced oxidative stress and mitochondrial dysfunction in human RPE (ARPE-19) cells in vitro.
MATERIALS AND METHODS: The ARPE-19 cells were divided into seven groups. Oxidative stress was triggered by incubating the ARPE-19 cells with 30 µM of 2-EP for 24 hours. Then, 200 µM of melatonin was administered over three days and 20 µM of MMT over six hours prior to the experiment. The effects of melatonin and MMT on the intracellular calcium release mechanism, reactive oxygen species production, caspase-3 and -9 activities, as well as vascular endothelial growth factor levels were measured.

RESULTS: Melatonin and MMT were found to significantly decrease apoptosis levels. The intracellular calcium release was regulated by both melatonin and MMT. Further, melatonin and MMT significantly decreased both caspase-3 and -9 activities, as well as pro-caspase and poly(ADP-ribose) polymerase expression, in ARPE-19 cells. Moreover, melatonin significantly increased the protective effect of MMT. The combination of melatonin and MMT significantly decreased 2-EP-induced oxidative toxicity and apoptosis by inhibiting the intracellular reactive oxygen species production and mitochondrial depolarization levels.

CONCLUSION: These notable findings are the first to demonstrate the synergistic protective effects of melatonin and MMT against 2-EP-induced oxidative stress in ARPE-19 cells.

PMID: 28707481


The formation of a functional retinal pigment epithelium occurs on porous polytetrafluoroethylene substrates independently of the surface chemistry.


Abstract: Subretinal transplantation of functioning retinal pigment epithelial (RPE) cells may have the potential to preserve or restore vision in patients affected by blinding diseases such as age-related macular degeneration (AMD). One of the critical steps in achieving this is the ability to grow a functioning retinal pigment epithelium, which may need a substrate on which to grow and to aid transplantation. Tailoring the physical and chemical properties of the substrate should help the engineered tissue to function in the long term. The purpose of the study was to determine whether a functioning monolayer of RPE cells could be produced on expanded polytetrafluoroethylene substrates modified by either an ammonia plasma treatment or an n-Heptylamine coating, and whether the difference in surface chemistries altered the extracellular matrix the cells produced. Primary human RPE cells were able to form a functional, cobblestone monolayer on both substrates, but the formation of an extracellular matrix to exhibit a network structure took months, whereas on non-porous substrates with the same surface chemistry, a similar appearance was observed after a few weeks. This study suggests that the surface chemistry of these materials may not be the most critical factor in the development of growth of a functional monolayer of RPE cells as long as the cells can attach and proliferate on the surface. This has important implications in the design of strategies to optimise the clinical outcomes of subretinal transplant procedures.

PMID: 28707136

J Lipid Res. 2017 Jul 11. [Epub ahead of print]

Plasma lipoprotein sub-fraction concentrations are associated with Lipid Metabolism and Age-related Macular Degeneration.

Cheung CMG, Gan A, Fan Q, Chee ML, Apte RS, Khor CC, Yeo I, Mathur R, Cheng CY, Wong TY, Tai ES.

Abstract: Disturbance in lipid metabolism has been suggested as a major pathogenic factor for age-related macular degeneration (AMD). Conventional lipid measures have been inconsistently associated with AMD. Other factors which can alter lipid metabolism include lipoprotein phenotype and genetic mutations. We performed a case-control study to examine the association between lipoprotein profile and neovascular
AMD (nAMD), and whether the cholesterylester transfer protein CETP D442G mutation modulates these associations. Patients with nAMD had significantly higher concentrations of HDL and IDL lipoprotein compared to controls. The increase in HDL lipoprotein particles in nAMD patients was driven by an excess of medium-sized particles. Concurrently, patients with nAMD also had lower apolipoprotein A-1, lower VLDL and chylomicron lipoprotein. Many of these associations showed a dose dependent association between controls, early AMD cases and nAMD cases. Adjustment for the presence of the D442G mutation at the CETP locus did not significantly alter the increased AMD risk associated with HDL particle concentration. AMD is associated with variation in many lipoprotein subclasses, including increased in HDL particles and IDL particles, and decreased Apo A-1, VLDL and chylomicron particles. These suggest widespread systemic disturbance in lipid metabolism in the pathogenesis of AMD, including possible alterations in lipoprotein carrier capacity.

PMID: 28698208

J Mol Neurosci. 2017 Jul 8. [Epub ahead of print]

Aerobic Glycolysis Hypothesis Through WNT/Beta-Catenin Pathway in Exudative Age-Related Macular Degeneration.

Vallée A, Lecarpentier Y, Guillevin R, Vallée JN.

Abstract: Exudative age-related macular degeneration (AMD) is characterized by molecular mechanisms responsible for the initiation of choroidal neovascularization (CNV). Inflammatory processes are associated with upregulation of the canonical WNT/beta-catenin pathway in exudative AMD. We focus this review on the link between WNT/beta-catenin pathway activation and neovascular progression in exudative AMD through activation of aerobic glycolysis for production of angiogenic factors. Increased WNT/beta-catenin pathway involves hexokinase 2 (HK2) and pyruvate kinase M2 (PKM2). WNT/beta-catenin pathway stimulates PI3K/Akt pathway and then HIF-1alpha which activates glycolytic enzymes: glucose transporter (Glut), pyruvate dehydrogenase kinase 1 (PDK1), lactate dehydrogenase A (LDH-A), and monocarboxylate lactate transporter (MCT-1). This phenomenon is called aerobic glycolysis or the Warburg effect. Consequently, phosphorylation of PDK-1 inhibits the pyruvate dehydrogenase complex (PDH). Thus, a large part of pyruvate cannot be converted into acetyl-CoA in mitochondria and only a part of acetyl-CoA can enter the tricarboxylic acid cycle. Cytosolic pyruvate is converted into lactate through the action of LDH-A. In exudative AMD, high level of cytosolic lactate is correlated with increase of VEGF expression, the angiogenic factor of CNV. Photoreceptors in retina cells can metabolize glucose through aerobic glycolysis to protect them against oxidative damage, as cancer cells do.

PMID: 28689265

Epidemiology

Ophthalmology. 2017 Jul 6. [Epub ahead of print]


PURPOSE: To conduct a nationwide survey on the prevalence and causes of vision loss in Indigenous and non-Indigenous Australians.

DESIGN: Nationwide, cross-sectional, population-based survey.
PARTICIPANTS: Indigenous Australians aged 40 years or older and non-Indigenous Australians aged 50 years and older.

METHODS: Multistage random-cluster sampling was used to select 3098 non-Indigenous Australians and 1738 Indigenous Australians from 30 sites across 5 remoteness strata (response rate of 71.5%). Sociodemographic and health data were collected using an interviewer-administered questionnaire. Trained examiners conducted standardized eye examinations, including visual acuity, perimetry, slit-lamp examination, intraocular pressure, and fundus photography. The prevalence and main causes of bilateral presenting vision loss (visual acuity <6/12 in the better eye) were determined, and risk factors were identified.

MAIN OUTCOME MEASURES: Prevalence and main causes of vision loss.

RESULTS: The overall prevalence of vision loss in Australia was 6.6% (95% confidence interval [CI], 5.4-7.8). The prevalence of vision loss was 11.2% (95% CI, 9.5-13.1) in Indigenous Australians and 6.5% (95% CI, 5.3-7.9) in non-Indigenous Australians. Vision loss was 2.8 times more prevalent in Indigenous Australians than in non-Indigenous Australians after age and gender adjustment (17.7%, 95% CI, 14.5-21.0 vs. 6.4%, 95% CI, 5.2-7.6, P < 0.001). In non-Indigenous Australians, the leading causes of vision loss were uncorrected refractive error (61.3%), cataract (13.2%), and age-related macular degeneration (10.3%). In Indigenous Australians, the leading causes of vision loss were uncorrected refractive error (60.8%), cataract (20.1%), and diabetic retinopathy (5.2%). In non-Indigenous Australians, increasing age (odds ratio [OR], 1.72 per decade) and having not had an eye examination within the past year (OR, 1.61) were risk factors for vision loss. Risk factors in Indigenous Australians included older age (OR, 1.61 per decade), remoteness (OR, 2.02), gender (OR, 0.60 for men), and diabetes in combination with never having had an eye examination (OR, 14.47).

CONCLUSIONS: Vision loss is more prevalent in Indigenous Australians than in non-Indigenous Australians, highlighting that improvements in eye healthcare in Indigenous communities are required. The leading causes of vision loss were uncorrected refractive error and cataract, which are readily treatable. Other countries with Indigenous communities may benefit from conducting similar surveys of Indigenous and non-Indigenous populations.

PMID: 28689897


Prevalence and Risk Factors for Nonexudative Neovascularization in Fellow Eyes of Patients With Unilateral Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy.

Yanagi Y, Mohla A, Lee WK, Lee SY, Mathur R, Chan CM, Yeo I, Wong TY, Cheung CMG.

PURPOSE: To determine the prevalence of subclinical nonexudative neovascularization and associated choroidal vascular changes in the fellow eyes of patients presenting with unilateral typical exudative AMD (tAMD) or polypoidal choroidal vasculopathy (PCV) using indocyanine green angiography (ICGA) and swept-source (SS) optical coherence tomography angiography (OCT-A).

METHODS: We recruited patients presenting with tAMD or PCV in a prospective clinical study. The diagnosis in the presenting eye was determined based on clinical, fluorescein angiography (FA), and ICGA findings. We evaluated the contralateral eye for presence of nonexudative neovascularization, choroidal hyperpermeability, and pachyvessels in the outer choroid, based on multimodal imaging which included ICGA, spectral-domain (SD) OCT and OCT-A. We measured subfoveal choroidal thickness in both eyes for each patient.

RESULTS: We included 76 fellow eyes of 76 patients who presented with unilateral tAMD (n = 33) or PCV (n = 43). Nonexudative neovascularization was present in 18% eyes (14 eyes, 8 in tAMD group, 6 in PCV group; 7 on ICGA, 4 on OCT-A, 3 on both ICGA and OCT-A). Pachychoroid pigment epitheliopathy was
present in 13 eyes with nonexudative neovascularization, and was the only risk factor associated with nonexudative neovascularization.

CONCLUSIONS: Approximately one in five fellow eyes with unilateral tAMD and PCV have features of nonexudative neovascularization. The use of multimodal imaging including ICGA and OCT-A can identify these features. The presence of pachychoroid epitheliopathy should alert clinicians to the possibility of underlying neovascularization.

PMID: 28702676

**Genetics**


**Genome-wide association study of neovascular age-related macular degeneration in the Thai population.**


Abstract: We performed a genome-wide association study on 377 cases of neovascular age-related macular degeneration (AMD) and 1074 controls to determine the association of previously reported genetic variants associated with neovascular AMD in the Thai population. All patients were of Thai ancestry. We confirmed the association of age-related maculopathy susceptibility 2 (ARMS2) rs10490924 (P=7.38 × 10^{-17}), HTRA1 rs11200638 (P=5.47 × 10^{-17}) and complement factor H gene (CFH) rs800292 (P=2.53 × 10^{-8}) with neovascular AMD, all loci passing the genome-wide significance level (P<5.22 × 10^{-8}). We also found association of the previously reported CFH rs10737680 (P=1.76 × 10^{-6}) locus in the discovery sample. Two loci not previously reported to be associated with neovascular AMD were selected for replication in 222 cases and 623 controls. The loci included LINCO1317 rs6733379 and rs2384550 on chromosome 12. LINCO1317 rs6733379 (P=3.85 × 10^{-2}) remained significantly associated with neovascular AMD after replication. In conclusion, we confirm that ARMS2, HTRA1 and CFH variants are associated with neovascular AMD in the Thai population. Findings from this study also suggest that variants contributing to the susceptibility of neovascular AMD in the Thai population are mostly similar to other Asians with additional local genetic risks that may specifically be identified in Thai population.

PMID: 28703135

**Invest Ophthalmol Vis Sci. 2017 Jul 1;58(9):3456-3463.**

**Report From the NEI/FDA Endpoints Workshop on Age-Related Macular Degeneration and Inherited Retinal Diseases.**

Csaky K, Ferris F 3rd, Chew EY, Nair P, Cheetham JK, Duncan JL.

PMID: 28702674

**Diet, lifestyle & low vision**


**Tracing the natural course of visual acuity and quality of life in neovascular age-related macular degeneration: a systematic review and quality of life study.**

Elshout M, Webers CA, van der Reis MI, de Jong-Hessey Y, Schouten JS.
BACKGROUND: Describing the natural course of neovascular age-related macular degeneration (nAMD) is essential in discussing prognosis and treatment options with patients and to support cost-effectiveness studies.

METHODS: First, we performed a literature search in PubMed, Embase, and Cochrane. We included randomized clinical trials and prospective observational studies reporting visual acuity (VA) in non-treated patients, 24 studies in total. We integrated VA data using best fit on Lineweaver-Burke plots and modelled with non-linear regression using reciprocal terms. Second, we performed a quality-of-life (QoL) study in nAMD patients. We measured VA with Radner reading charts and QoL with the Health Utilities Index issue 3 (HUI-3) questionnaire in 184 participants. We studied the relation VA-QoL with linear regression. Third, with Monte Carlo simulation, we integrated the VA model from the literature review and the relation VA-QoL from the QoL study.

RESULTS: Visual acuity was 0.4 and 0.07 after 5 years in the better-seeing, and worse-seeing eye, respectively. After 4.3 years, VA was <0.5 in the better-seeing eye; <0.3 after 7 years; 0.05 after 17 years. QoL score decreased from 0.6 to 0.45 after 10 years.

CONCLUSIONS: The natural course of nAMD in both eyes needs to be considered when informing patients. Visual acuity in the best eye decreases to below 0.5 in 4.3 years. This affects QoL significantly.

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