Macular Disease Foundation AUSTRALIA
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Drug treatment

JAMA Ophthalmol. 2014 May 29. doi: 10.1001/jamaophthalmol.2014.1019. [Epub ahead of print]

Sustained Visual Acuity Loss in the Comparison of Age-Related Macular Degeneration Treatments Trials.

Ying GS, Kim BJ, Maguire MG, Huang J, Daniel E, Jaffe GJ, Grunwald JE, Blinder KJ, Flaxel CJ, Rahhal F, Regillo C, Martin DF; for the CATT Research Group.

IMPORTANCE: Although anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration (AMD) results in improved vision overall, loss of substantial vision can occur. Understanding the processes that lead to loss of vision may lead to preventive strategies.

OBJECTIVE: To determine the incidence, characteristics, causes, and baseline predictors of sustained visual acuity loss after 2 years of treatment with ranibizumab or bevacizumab for neovascular AMD.

DESIGN, SETTING, AND PARTICIPANTS: A cohort study within a randomized clinical trial of participants in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

INTERVENTIONS: Participants were randomly assigned to treatment with ranibizumab or bevacizumab and to 2 years of monthly or as needed injections or monthly injections for 1 year and as needed injections the following year.

MAIN OUTCOMES AND MEASURES: Sustained visual acuity loss, defined as loss of 15 or more letters from baseline at weeks 88 and 104.

RESULTS: Among 1030 participants, 61 eyes (5.9%) developed sustained visual acuity loss in 2 years. Within this group, visual acuity decreased gradually over time, with a mean decrease of 2, 19, and 33 letters from baseline at 4 weeks, 1 year, and 2 years, respectively. At 2 years, eyes with sustained visual acuity loss had more scarring (60.0% vs 41.4%, P = .007), more geographic atrophy (GA) (31.6% vs 20.7%, P = .004), larger lesions (16 vs 8 mm2, P < .001), and higher proportions of intraretinal fluid (82.5% vs 51.0%, P < .001), subretinal hyperreflective material (84.5% vs 44.2%, P < .001), retinal thinning (43.3% vs 23.0%, P < .001), and thickening (20.0% vs 12.1%, P < .001). Likely causes of sustained visual acuity loss included foveal scarring (44.3%), pigmentary abnormalities (27.9%), and foveal GA (11.5%). Baseline factors independently associated with a higher incidence of sustained visual acuity loss were the presence of nonfoveal GA (odds ratio [OR], 2.86; 95% CI, 1.35-6.08; P = .006), larger area of choroidal neovascularization (OR for a >4-disc area vs ≤1-disc area, 3.91; 95% CI, 1.70-9.03; P = .007), and bevacizumab treatment (OR, 1.83; 95% CI, 1.07-3.14; P = .03).

CONCLUSIONS AND RELEVANCE: Sustained visual acuity loss was relatively rare in CATT. The development of foveal scar, pigmentary abnormalities, or GA contributed to most of the sustained visual

acuity loss. Risk was 3% higher among eyes treated with bevacizumab. Treatment that targeted the prevention of scarring or GA may improve vision outcomes.

PMID: 24875610 [PubMed - as supplied by publisher]

Retina. 2014 May 22. [Epub ahead of print]

RETINA SPECIALISTS TREATING AGE-RELATED MACULAR DEGENERATION RECOMMEND DIFFERENT APPROACHES FOR PATIENTS THAN THEY WOULD CHOOSE FOR THEMSELVES.

Jeng KW, Wilgucki J, Halperin S, Feuer WJ, Fine HF, Roth D, Prenner JL.

PURPOSE: To evaluate the presence of cognitive biases among retina physicians when recommending treatment options for exudative age-related macular degeneration.

METHODS: Two random samples of retina specialists were surveyed regarding their treatment and dosing regimen choices among three anti-vascular endothelial growth factor biologics (aflibercept, bevacizumab, and ranibizumab). One group was asked to provide recommendations for a standardized hypothetical patient with exudative age-related macular degeneration, whereas the other group was asked to provide recommendations as if they themselves were the standardized hypothetical patient with exudative age-related macular degeneration.

RESULTS: Two hundred and twenty-six respondents (28.3%) completed the survey and were divided equally between the survey groups. For patients, most physicians recommended bevacizumab (52.2%), but when choosing for themselves, physicians were divided equally among all 3 biologics (P = 0.011). The results were influenced by geographical location of the physician but not by the gender or length of practice. Furthermore, physicians differed in dosing regimen selection with the majority (73%) choosing treat and extend for patients, whereas only 63% selected this regimen for themselves (P = 0.004).

CONCLUSION: When considering cases of exudative age-related macular degeneration, physicians would recommend different treatments for themselves than they would for a patient.

PMID: 24859475 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 May 28. pii: S0002-9394(14)00297-9. doi: 10.1016/j.ajo.2014.05.025. [Epub ahead of print]

Suppression of Intraocular Vascular Endothelial Growth Factor During Aflibercept Treatment of Age -Related Macular Degeneration.

Fauser S, Schwabecker V, Muether PS.

PURPOSE: To determine the duration of suppression of aqueous humor concentrations of vascular endothelial growth factor (VEGF) in eyes with neovascular age-related macular degeneration (AMD) treated with aflibercept.

DESIGN: Nonrandomized prospective clinical study.

METHODS: Twenty-seven eyes of 27 neovascular AMD patients receiving intravitreal aflibercept injections on a pro re nata regimen driven by spectral-domain optical coherence tomography (SD-OCT) were included in this study. A total of 132 aqueous humor specimens were collected before intravitreal aflibercept injections, and their VEGF-A concentrations assayed by Luminex multiplex bead analysis (Luminex Inc., Austin, TX).

RESULTS: Mean aqueous humor VEGF concentrations before treatment initiation were 90.6 ± 37.1 pg/ml

(range 23.4 - 190.3 pg/ml). Intravitreal injection of aflibercept suppressed the aqueous VEGF concentrations to below the lower limit of quantification (<4pg/ml) in all patients. The mean duration of VEGF suppression below the lower limit of quantification was >71 ± 18 days. The earliest time after injection at which the VEGF concentration recovered to above the lower limit of quantification was 55 days in one patient; and >56 days, the recommended aflibercept treatment interval in 20 patients. The aqueous VEGF recovery status of six patients was uncertain after 56 days.

CONCLUSIONS: On average, VEGF concentrations in the aqueous humor were suppressed below the lower limit of quantification after intravitreal aflibercept injections for about 10 weeks. This aqueos suppression time suggests durable VEGF inhibition for most patients dosed with aflibercept every 8 weeks.

PMID: 24879948 [PubMed - as supplied by publisher]

Curr Eye Res. 2014 May 28:1-6. [Epub ahead of print]

The Effect of Multiple Injections of Ranibizumab on Retinal Nerve Fiber Layer Thickness in Patients with Age-Related Macular Degeneration.

Demirel S, Batıoğlu F, Ozmert E, Erenler F.

Abstract Purpose: To evaluate the effects of multiple intravitreal injections of ranibizumab on retinal nerve fiber layer (RNFL) thickness in patients with wet age-related macular degeneration (AMD).

Methods: This observational, comparative study included patients with 10 or more total ranibizumab injections and involved the measurement of RNFL thickness at baseline. Twenty-nine eyes of 29 consecutive patients were evaluated via intraocular pressure (IOP) and measurements of the total and nasal RNFL thicknesses at the initial and final follow-up by using optical coherence tomography. The RNFL thickness values of the fellow eyes and 27 healthy eyes were used as the control group. The mean total and nasal RNFL thicknesses of the injection group were compared with those of the other two groups. At each visit, at every three injections, the IOP values of the study group were recorded and compared. The relationship between the number of injections and the mean RNFL thickness was assessed.

Results: The mean number of injections was 13.88 ± 3.81 (10-24). The mean RNFL thickness of the injection group was 92.3 ± 7.7 μm at baseline and 92.46 ± 8.1 μm at the last follow-up ($p = 0.7$). There were no statistically significant differences between the mean total and nasal RNFL thicknesses of the eyes with injections and the fellow eyes with no injections ($p = 0.379$, $p = 0.897$, respectively) or between those with injections and the healthy control group ($p = 0.159$, $p = 0.273$, respectively). There were no correlations between the number of injections and the mean total and nasal RNFL thicknesses ($p = 0.854$, $p = 0.25$, respectively). There was no statistical difference between the initial and final IOPs ($p = 0.760$).

Conclusion: Long-term treatment with anti-vascular endothelial growth factor (VEGF) agents did not lead to significant changes in RNFL thickness in a patient population with wet AMD. Chronic therapy with intravitreal anti-VEGF agents does not appear to adversely affect RNFL thickness.

PMID: 24871814 [PubMed - as supplied by publisher]

J Ophthalmol. 2014;2014:857148. doi: 10.1155/2014/857148. Epub 2014 Apr 28.

A 2-Year, Phase IV, Multicentre, Observational Study of Ranibizumab 0.5 mg in Patients with Neovascular Age-Related Macular Degeneration in Routine Clinical Practice: The EPICOHORT Study.

Pagliarini S, Beatty S, Lipkova B, Perez-Salvador Garcia E, Reynders S, Gekkieva M, Si Bouazza A, Pilz S.

Purpose: To assess the safety profile of ranibizumab 0.5 mg in patients with neovascular age-related

macular degeneration (nAMD) in routine clinical practice.

Methods: This 2-year, multicentre, observational study was conducted to capture real-world early practice and outcomes across Europe, shortly after European licensing of ranibizumab for nAMD. Being observational in nature, the study did not impose diagnostic/therapeutic interventions/visit schedule. Patients were to be treated as per the EU summary of product characteristics (SmPC) in effect during the study. Key outcome measures were incidence of selected adverse events (AEs), treatment exposure, bilateral treatment, compliance to the EU SmPC, and best-corrected visual acuity (BCVA) over 2 years.

Results: 755 of 770 patients received treatment. Ranibizumab was generally well tolerated with low incidence of selected AEs (0%-1.9%). Patients received 6.2 (mean) injections and 133 patients received bilateral treatment over 2 years. Protocol deviation to treatment compliance was reported in majority of patients. The observed decline in mean BCVA (Month 12, +1.5; Month 24, -1.3 letters) may be associated with undertreatment as suggested by BCVA subgroup analysis.

Conclusion: The EPICOHORT study conducted in routine clinical practice reinforces the well-established safety profile of ranibizumab in nAMD. In early European practice it appeared that the nAMD patients were undertreated.

PMID: 24868458 [PubMed] PMCID: PMC4020221

Am J Ophthalmol. 2014 May 20. pii: S0002-9394(14)00248-7. doi: 10.1016/j.ajo.2014.05.014. [Epub ahead of print]

Anti-VEGF Treatment Patterns for Neovascular Age-Related Macular Degeneration Among Medicare Beneficiaries.

Lad EM, Hammill BG, Qualls LG, Wang F, Cousins SW, Curtis LH.

PURPOSE: To examine the use of anti-vascular endothelial growth factor (VEGF) therapy in clinical practice among patients with neovascular age-related macular degeneration (AMD).

DESIGN: Retrospective cohort study.

METHODS: Among 459,237 Medicare beneficiaries, we identified anti-VEGF treatment using claims for intravitreal injections of anti-VEGF medications with a supporting diagnosis of neovascular AMD. We used the cumulative incidence function to calculate the frequency of anti-VEGF treatments and treatment visits for neovascular AMD per treated eye in the first and second year after the initial anti-VEGF injection. We calculated the mean number of treatments and treatment visits per eye using the mean frequency function. Rates of discontinuation were estimated using Kaplan-Meier methods.

RESULTS: The mean number of injections was 4.3 in the first year, with 58% of patients receiving 1 to 4 injections, 20% receiving 5 to 6 injections, and 22% receiving 7 or more injections. Among patients who received 7 or more injections during the first year, 31% received a comparable number during the second year, and 12% received no injections. Of patients who received 1 to 4 injections during the first year, 70% received no injections and 24% received 1 to 4 injections during the second year. Rates of anti-VEGF discontinuation were 57% within 12 months and 71% within 24 months.

CONCLUSIONS: The frequency of anti-VEGF injections for neovascular AMD was lower than that recommended by large-scale clinical trials, and rates of discontinuation were high. National practice patterns in anti-VEGF therapy for patients with neovascular AMD do not reflect optimal treatment strategies suggested by recent clinical trial evidence.

PMID: 24857687 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2014 Jun;49(3):261-6. doi: 10.1016/j.jcjo.2014.03.009.

Survey of intravitreal injection techniques and treatment protocols among retina specialists in Canada.

Xing L, Dorrepaal SJ, Gale J.

OBJECTIVE: To describe intravitreal injection (IVI) techniques and treatment protocols by retina specialists in Canada from August 1, 2012, to October 1, 2012.

DESIGN: Cross-sectional survey.

PARTICIPANTS: All fellowship-trained retina specialists across Canada, as identified from the Canadian Ophthalmological Society directory and the Canadian Retina and Vitreous Society directory.

METHODS: An anonymous 28-question survey was sent to 125 retina specialists across Canada by email. Reminder letters were sent by email, mail, and fax as necessary.

RESULTS: A total of 75 (63%) retina specialists responded to the survey. Most IVIs were performed in the office. Most surgeons did not use gloves (61%), sterile draping (91%), or surgical mask (71%). Antisepsis was used on conjunctiva by 100% and on periocular skin by 48%. Nearly all specialists used a sterile lid speculum (91%). Common anaesthetics included topical proparacaine or lidocaine drops (90%), topical lidocaine gel (25%), topical pledget (23%), and subconjunctival lidocaine injections (23%). Most (83%) dilate the pupil before IVI. Prophylactic topical antibiotics were used by 43%; 50% of these were started immediately after IVI. Injection location was estimated by visualization by 45%. A majority (63%) inject inferotemporally. Anterior chamber paracentesis was performed routinely by 5%. Optic nerve perfusion was formally assessed by 48%. The most common treatment protocol for age-related macular degeneration was treat and extend. For both diabetic and retinal vein occlusion-related macular edema, the most common protocol was 3 initial monthly injections with PRN follow-up.

CONCLUSIONS: A wide variety of IVI practice patterns exist in terms of aseptic technique, anaesthetics, prophylactic antibiotics, postinjection monitoring, and treatment protocol.

PMID: 24862772 [PubMed - in process]

Optom Vis Sci. 2014 May 29. [Epub ahead of print]

Trends in Age-Related Macular Degeneration Management in Singapore.

Ng WY, Cheung CM, Mathur R, Chan CM, Yeo IY, Wong E, Lee SY, Loh BK, Wong D, Wong TY.

PURPOSE: To describe the trends and patterns of anti-vascular endothelial growth factor (anti-VEGF) therapy and photodynamic therapy (PDT) use for age-related macular degeneration (AMD) in the National Eye Centre in Singapore over a 4-year period.

METHODS: Data on the total number of intravitreal anti-VEGF injections and PDT treatment over a 4-year period at the Singapore National Eye Centre were obtained from centralized electronic records. Patients aged 40 years and older treated for AMD were included. Data retrieved included the annual treatment load in terms of number of new patients and total treatment episodes, and treatment burden for patients was studied in terms of number of injections per year and cumulative injection numbers over 3 years. Potential influence on retreatment by choice of drug, use of adjunct PDT, and diagnosis of polypoidal choroidal vasculopathy were further analyzed.

RESULTS: From 2009 to 2012, a total of 6157 injections were performed on 1380 unique individual patients. The total number of injections performed per calendar year increased from 962 in 2009 to 2278 in 2012. The number of unique incident cases increased from 287 in 2009 to 446 in 2012. The mean number of injections over the first year increased from 2.62 in 2009 to 3.19 in 2012 ($p < 0.001$). Choice of anti-

VEGF therapy did not significantly alter the cumulative injections required. Patients diagnosed as having polypoidal choroidal vasculopathy had similar injection episodes (p = 0.178), whereas choice of anti-VEGF and adjunct PDT had no effect on the overall treatment.

CONCLUSIONS: Anti-VEGF treatment of AMD continues to increase substantially year on year in the past few years, in alignment with experience from other countries. However, the cumulative number of injections per patient remains low, and many patients discontinue treatment within the first year. These data demonstrate that undertreatment remains a significant concern in clinical settings.

PMID: 24879088 [PubMed - as supplied by publisher]

J Ophthalmol. 2014;2014:382702. doi: 10.1155/2014/382702. Epub 2014 Apr 27.

Clinical efficacy of intravitreal ranibizumab in early and mid-idiopathic choroidal neovascularization.

Fan C, Ji Q, Wang Y, Shu X, Xie J.

Background: To compare visual outcomes and spectral-domain optical coherence tomography results following intravitreal ranibizumab treatment for early and mid-idiopathic choroidal neovascularization (ICNV).

Methods: This retrospective, case-controlled study examined 44 patients with ICNV in one eye initially treated with intravitreal ranibizumab (0.5 mg). Further intravitreal treatments were administered as necessary. Patients were divided into two groups according to disease duration, that is, ≤3 months or 3-6 months (early and mid-groups), and the data were compared.

Results: All patients completed at least 12 months of follow-up. Significant differences were observed between the groups in best-corrected visual acuity and in central macular thickness (CMT) reduction at all five follow-up visits. At the last follow-up (12 months), 19 early group eyes (79.1%) and 10 mid group eyes (50.0%) had statistically significant visual gains of >15 early treatment diabetic retinopathy study (ETDRS) letters (χ (2) = 4.130, P = 0.042). The mean number of injections was significantly higher (P = 0.0001) in the mid group (2.53 ± 1.76) than in the early group (1.22 ± 1.01).

Conclusions: Early intravitreal ranibizumab for ICNV can result in better visual prognoses, more obvious decreases in CMT, and fewer injections.

PMID: 24868452 [PubMed] PMCID: PMC4020209

Med Sci Monit. 2014 May 28;20:875-83. doi: 10.12659/MSM.890031.

Influence of ranibizumab treatment on the extracellular matrix in patients with neovascular age-related macular degeneration.

Nita M, Michalska-Małecka K, Mazurek U, Kimsa M, Strzałka-Mrozik B, Grzybowski A, Romaniuk D.

Background: We know the influence of the intravitreal anti-vascular endothelial growth factor (VEGF) injections on the choroidal neovascularization in the course of exudative age-related macular degeneration (AMD). However, the influence of the ranibizumab therapy in question on the extracellular matrix (ECM) remains unknown. We aimed to estimate the influence of Lucentis intravitreal injections on the gene expression of structural components of the extracellular matrix in patients with neovascular AMD

Material and Methods: Patients with subfoveal localization of neovascularization in AMD, which was clinically active and observed using optical coherence tomography, were treated with ranibizumab (0.5 mg/0.05 mL) in accordance with the PrONTO scheme. Total RNA was extracted from peripheral blood

mononuclear cells, and an oligonucleotide microarray technique enabled comparison of the expression level of genes encoding collagens, elastin, and laminins in AMD patients compared to control subjects.

Results: After 3 intravitreal injections of ranibizumab (Lucentis), COL1A1 and COL6A1 genes showed increased expression, whereas decreased expression mainly occurred for the following genes: COL4A5, COL11A1, OL4A6C, LAMB4, and LAMC2.

Conclusions: Anti-VEGF local therapy influences the gene expression of structural components of the ECM as measured from blood samples. The loading dose of ranibizumab for the retina changes the expression of collagen and laminin genes, but does not influence the expression of the elastin gene.

PMID: 24866589 [PubMed - in process]

J Ophthalmol. 2014;2014:450428. Epub 2014 Apr 27.

Management of Uveitis-Related Choroidal Neovascularization: From the Pathogenesis to the Therapy.

D'Ambrosio E, Tortorella P, Iannetti L.

Abstract: Inflammatory choroidal neovascularization is a severe but uncommon complication of uveitis, more frequent in posterior uveitis such as punctate inner choroidopathy, multifocal choroiditis, serpiginous choroiditis, and Vogt-Koyanagi-Harada syndrome. Its pathogenesis is supposed to be similar to the wet age related macular degeneration: hypoxia, release of vascular endothelial growth factor, stromal cell derived factor 1-alpha, and other mediators seem to be involved in the uveitis-related choroidal neovascularization. A review on the factors implicated so far in the pathogenesis of inflammatory choroidal neovascularization was performed. Also we reported the success rate of single studies concerning the therapies of choroidal neovascularization secondary to uveitis during the last decade: photodynamic therapy, intravitreal bevacizumab, and intravitreal ranibizumab, besides steroidal and immunosuppressive therapy. Hereby a standardization of the therapeutic approach is proposed.

PMID: 24868454 [PubMed - as supplied by publisher] PMCID: PMC4020300

JAMA. 2014 May 23. doi: 10.1001/jama.2014.6672. [Epub ahead of print]

Drugs for Macular Degeneration, Price Discrimination, and Medicare's Responsibility Not to Overpay.

Silver J.

PMID: 24860863 [PubMed - as supplied by publisher]

Expert Opin Drug Metab Toxicol. 2014 May 24:1-8. [Epub ahead of print]

Pharmacokinetic evaluation of pegaptanib octasodium for the treatment of diabetic edema.

Morjaria R, Chong NV.

Introduction: Diabetic macular edema (DME) is a leading cause of visual impairment in patients with diabetic retinopathy. Pegaptanib octasodium (Macugen) was the first anti-VEGF agent approved for the treatment of neovascular age-related macular degeneration. It is a selective anti-VEGF agent, which only blocks VEGF. It has been shown to be safe and effective in treatment of DME in randomized controlled trials and it may be a safer first-line treatment in patients with diabetes with a predisposition to cardiovascular risk factors.

Areas covered: This review covers the pharmacokinetics of pegaptanib octasodium. The authors also evaluate pegaptanib octasodium's clinical efficacy, safety and tolerability in DME.

Expert opinion: DME is the most common cause of visual loss in patients with diabetes. Pegaptanib has been found to be more effective than laser therapy alone for center-involving DME, its efficacy might be slightly worse than other pan-VEGF blockers, but the number of patients that have significant improvement of vision after treatment are similar to those treated with pan-VEGF blockers. As a selective VEGF blocker, it may have a better ocular and systemic safety profile than pan-VEGF blocking agents. It is reasonable to consider pegaptanib as the first-line treatment for center-involving DME with pan-VEGF blockers reserved for non-responders.

PMID: 24856361 [PubMed - as supplied by publisher]

F1000Prime Rep. 2014 May 6;6:29. eCollection 2014.

Advances in the management of macular degeneration.

Singer M.

Abstract: Current management of age-related macular degeneration (AMD) can be divided into two categories: first, anti-vasoendothelial growth factor (anti-VEGF) injection for wet macular degeneration; second, anti-oxidant vitamins for dry macular degeneration. New therapies are being developed for both of these diseases using novel technologies and different modes of administration. The hope is that some of these therapies will achieve significant improvement to current management and prevent future loss of vision in this devastating eye condition.

PMID: 24860651 [PubMed - as supplied by publisher] PMCID: PMC4017905

Other treatment & diagnosis

Ophthalmology. 2014 May 21. pii: S0161-6420(14)00239-5. doi: 10.1016/j.ophtha.2014.03.015. [Epub ahead of print]

Clinical Characteristics of Reticular Pseudodrusen in the Fellow Eye of Patients with Unilateral Neovascular Age-Related Macular Degeneration.

Hogg RE, Silva R, Staurenghi G, Murphy G, Santos AR, Rosina C, Chakravarthy U.

PURPOSE: To describe associations between reticular pseudodrusen, individual characteristics, and retinal function.

DESIGN: Cohort study.

PARTICIPANTS: We recruited 105 patients (age range, 52-93 years) who had advanced neovascular age-related macular degeneration (AMD) in only 1 eye from 3 clinical centers in Europe.

METHODS: Minimum follow-up was 12 months. The eye selected for study was the fellow eye without advanced disease. Clinical measures of vision were distance visual acuity, near visual acuity, and results of the Smith-Kettlewell low-luminance acuity test (SKILL). Fundus imaging included color photography, red-free imaging, blue autofluorescence imaging, fluorescein angiography, indocyanine green angiography, and optical coherence tomography using standardized protocols. These were used to detect progression to neovascular AMD in the study eye during follow-up. All imaging outputs were graded for the presence or absence of reticular pseudodrusen (RPD) using a multimodal approach. Choroidal thickness was measured at the foveal center and at 2 other equidistant locations from the fovea (1500 μm) nasally and temporally. Metrics on retinal thickness and volume were obtained from the manufacturer-supplied automated

segmentation readouts.

MAIN OUTCOME MEASURES: Presence of RPD, distance visual acuity, near visual acuity, SKILL score, choroidal thickness, retinal thickness, and retinal volume.

RESULTS: Reticular pseudodrusen was found in 43 participants (41%) on 1 or more imaging method. The SKILL score was significantly worse in those with reticular drusen (mean score ± standard deviation [SD, 38±12) versus those without (mean score ± SD, 33±9) (P = 0.034). Parafoveal retinal thickness, parafoveal retinal volume, and all of the choroidal thickness parameters measured were significantly lower in those with reticular drusen than in those without. The presence of RPD was associated with development of neovascular AMD when corrected for age and sex (odds ratio, 5.5; 95% confidence interval, 1.1-28.8; P = 0.042). All participants in whom geographic atrophy developed during follow-up had visible RPD at baseline.

CONCLUSIONS: Significant differences in retinal and choroidal anatomic features, visual function, and risk factor profile exist in unilateral neovascular AMD patients with RPD compared with those without; therefore, such patients should be monitored carefully because of the risk of developing bilateral disease.

PMID: 24856310 [PubMed - as supplied by publisher]

Optom Vis Sci. 2014 May 22. [Epub ahead of print]

Human Pluripotent Stem Cell Strategies for Age-Related Macular Degeneration.

Davidson KC, Guymer RH, Pera MF, Pébay A.

Abstract: Age-related macular degeneration (AMD) is a leading cause of severe vision loss in the Western world and is increasing exponentially as the population ages. Despite enormous worldwide efforts, the earliest pathogenic pathways involved in AMD are still not fully understood. It is essential to develop research tools for effective modeling of AMD pathogenesis and for subsequent drug discovery and cell or molecular therapies. This review will focus on the current progress in human pluripotent stem cells for understanding and treating AMD.

PMID: 24859130 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 May 20. pii: S0002-9394(14)00247-5. doi: 10.1016/j.ajo.2014.05.013. [Epub ahead of print]

Radial versus raster spectral-domain optical coherence tomography scan patterns for detection of macular pathology.

Rahimy E, Rayess N, Maguire JI, Hsu J.

PURPOSE: To compare the 6-line radial versus the 25-line raster spectral-domain optical coherence tomography (SD-OCT) acquisition patterns at detecting intraretinal fluid, subretinal fluid, vitreomacular traction, and full-thickness macular hole (MH).

DESIGN: Retrospective cross-sectional analysis.

METHODS: Series of 365 eyes with neovascular age-related macular degeneration (AMD), diabetic macular edema (DME), central and branch retinal vein occlusion (CRVO/BRVO), central serous chorioretinopathy, vitreomacular traction, and full-thickness MH. Sequential 6-line radial and 25-line raster scans were evaluated for intraretinal/subretinal fluid and when applicable, vitreomacular traction and MH.

RESULTS: For neovascular AMD (133 scans), seven 25-line raster scans confirmed subretinal/intraretinal

fluid not identified by the 6-line radial (P=0.02). For DME (140 scans) and central serous chorioretinopathy (91 scans), 25-line raster confirmed fluid in four scans (P=0.13) and one scan (P=0.32), respectively, that was not observed with the 6-line radial. For CRVO (123 scans) and BRVO (126 scans), 25-line raster confirmed fluid on two (P=0.25) and four scans (P=0.13), respectively, that was not detected by the 6-line radial. Conversely, for focal vitreomacular traction (70 scans) and full-thickness MH (82 scans), 25-line raster missed focal traction (<1500 microns) and MH in five scans (P=0.07) and seven scans (P=0.02), respectively, that were identified using the 6-line radial.

CONCLUSIONS: The 6-line radial scan is statistically comparable to the 25-line raster at detecting fluid in DME, BRVO/CRVO, and central serous chorioretinopathy, but not neovascular AMD. Furthermore, it is superior to the 25-line raster pattern at detecting early MH formation, while demonstrating a positive trend in identifying focal vitreomacular traction.

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Am J Ophthalmol. 2014 May 28. pii: S0002-9394(14)00298-0. doi: 10.1016/j.ajo.2014.05.026. [Epub ahead of print]

A Longitudinal Comparison of Spectral-Domain Optical Coherence Tomography and Fundus Autofluorescence in Geographic Atrophy.

Simader C, Sayegh RG, Montuoro A, Alzahary M, Koth AL, Baratsits M, Sacu S, Prünte C, Kreil DP, Schmidt-Erfurth U.

PURPOSE: To identify reliable criteria based on spectral-domain optical coherence tomography (SD-OCT) to monitor disease progression in geographic atrophy due to age-related macular degeneration (AMD) compared with lesion size determination based on fundus autofluorescence (FAF).

DESIGN: Prospective longitudinal observational study METHODS: Setting:Institutional.

STUDY POPULATION: A total of 48 eyes in 24 patients with geographic atrophy.

OBSERVATION PROCEDURES: Eyes with geographic atrophy were included and examined at baseline and months 3, 6, 9 and 12. At each study visit best-corrected visual acuity (BCVA), FAF and SD-OCT imaging using a Spectralis HRA + OCT System were performed. FAF images were analyzed using the region overlay device. Planimetric measurements in SD-OCT including alterations or loss of outer retinal layers and the RPE as well as choroidal signal enhancement were performed with the OCT Toolkit.

MAIN OUTCOME MEASURES: Areas of interests in patients with geographic atrophy measured from baseline to month 12 by SD-OCT compared with the area of atrophy measured by FAF.

RESULTS: Geographic atrophy lesion size increased from 8.88 mm^2 to 11.22 mm^2 based on quantitative FAF evaluation. Linear regression analysis demonstrated that results similar to FAF planimetry for determining lesion progression can be obtained by measuring the areas of outer plexiform layer thinning (adjusted R2 = 0.93), external limiting membrane loss (adjusted R2 = 0.89), or choroidal signal enhancement (R2 = 0.93) by SD-OCT.

CONCLUSIONS: SD-OCT allows morphologic markers of disease progression to be identified in geographic atrophy and may improve understanding of the pathophysiology of atrophic AMD.

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Optom Vis Sci. 2014 May 29. [Epub ahead of print]

Age-Related Macular Degeneration: Linking Clinical Presentation to Pathology.

Nivison-Smith L, Milston R, Madigan M, Kalloniatis M.

Abstract: Age-related macular degeneration (AMD) is one of the leading causes of blindness worldwide in the elderly population. Optometrists, as primary eye health care providers, require the skills and knowledge to accurately diagnose and manage AMD patients. There is an overwhelming body of research related to the clinical presentation, etiology, epidemiology, and pathology of this disease. Additionally, the evolution of new imaging modalities creates new opportunities to clinically detect and analyze previously uncharacterized and earlier changes in the retina. The challenge for optometrists is to combine all this information into an applicable knowledge base for use in everyday clinical assessment of AMD so that timely and accurate referrals can be made to retinal specialists. This review attempts to address this issue by linking the clinical presentation of AMD with the underlying disease biology. We emphasize the contribution of recent noninvasive imaging technologies to the clinical assessment of early and more advanced AMD including optical coherence tomography, fundus autofluorescence, and infrared reflectance.

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Ophthalmology. 2014 May 23. pii: S0161-6420(14)00310-8. doi: 10.1016/j.ophtha.2014.03.036. [Epub ahead of print]

Vitreoretinal Interface Changes in Geographic Atrophy.

Abdillahi H, Enzmann V, Wittwer VV, Wolf S, Wolf-Schnurrbusch UE.

PURPOSE: Geographic atrophy (GA) is the end-stage manifestation of atrophic age-related macular degeneration (AMD). The disease progresses slowly over time, eventually causing loss of central vision. Its cause and pathomechanism are not fully known. Previous studies have suggested that vitreoretinal traction (VRT) may contribute to the progression of neovascular AMD. The aim of this study was to examine whether an association between changes at the vitreoretinal interface (VRI), in particular traction (VRT), and the characteristics and progression of GA in eyes with dry AMD can be established.

DESIGN: Clinic-based prospective cohort study.

PARTICIPANTS: A total of 97 patients (age range, 61-90 years; mean, 78.4 years) with GA secondary to dry AMD were enrolled. Patients exhibiting neovascular signs on fluorescein angiography in either eye were excluded.

METHODS: The VRI changes were examined using spectral-domain optical coherence tomography (SD-OCT). Characteristics of GA were examined using fundus autofluorescence (FAF) imaging. All imaging was performed using a Spectralis SLO+OCT device (Heidelberg Engineering, Heidelberg, Germany); GA area was measured using the Region Finder (Heidelberg Engineering) software native to the Spectralis platform.

MAIN OUTCOME MEASURES: Area and increase in area of GA.

RESULTS: A total of 97 eyes were examined. Vitreoretinal traction was found in 39 eyes (40%). The GA area at baseline was 6.65±5.64 mm2 in eyes with VRT and 5.73±4.72 mm2 in eyes with no VRT. The annual rate of progression of GA area progression was 2.99±0.66 mm2 in eyes with VRT and 1.45±0.67mm2 in eyes without VRT. Differences between groups in both parameters were statistically significant (n = 97 total number of eyes; $P<0.001$). Multiple regression analysis confirmed this finding ($B = 0.714$, $P<0.001$; $F3,93 = 72.542$, $P<0.001$; adjusted $R2 = 0.691$) CONCLUSIONS: Our results indicate an association between VRT and an increased rate of progression of GA area in dry AMD. Monitoring VRT may contribute to an improved estimate of the prospective time of visual loss and to a better timing of emerging therapies in dry AMD.

PMID: 24863462 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2014 May 29. doi: 10.1001/jamaophthalmol.2014.1051. [Epub ahead of print]

Effect of a Teleretinal Screening Program on Eye Care Use and Resources.

Chasan JE, Delaune B, Maa AY, Lynch MG.

IMPORTANCE: Telemedicine is a useful clinical method to extend health care to patients with limited access. Minimal information exists on the subsequent effect of telemedicine activities on eye care resources.

OBJECTIVE: To evaluate the effect of a community-based diabetic teleretinal screening program on eye care use and resources.

DESIGN, SETTING, AND PARTICIPANTS: The current study was a retrospective medical record review of patients who underwent diabetic teleretinal screening in the community-based clinics of the Atlanta Veterans Affairs Medical Center from October 1, 2008, through March 31, 2009, and who were referred for an ophthalmic examination in the eye clinic.

EXPOSURES: Clinical medical records were reviewed for a 2-year period after patients were referred from teleretinal screening. The following information was collected for analysis: patient demographics, referral and confirmatory diagnoses, ophthalmology clinic visits, diagnostic procedures, surgical procedures, medications, and spectacle prescriptions.

MAIN OUTCOMES AND MEASURES: The accuracy between referring and final diagnoses and the eye care resources that were used in the care of referred patients.

RESULTS: The most common referral diagnoses were nonmacular diabetic retinopathy (43.2%), nerve-related disease (30.8%), lens or media opacity (19.1%), age-related macular degeneration (12.9%), and diabetic macular edema (5.6%). The percentage of agreement among these 5 visually significant diagnoses was 90.4%, with a total sensitivity of 73.6%. Diabetic macular edema required the greatest number of ophthalmology clinic visits, diagnostic tests, and surgical procedures. Using Medicare cost data estimates, the mean cost incurred during a 2-year period per patient seen in the eye clinic was approximately $1000.

CONCLUSIONS AND RELEVANCE: Although a teleretinal screening program can be accurate and sensitive for multiple visually significant diagnoses, measurable resource burdens should be anticipated to adequately prepare for the associated increase in clinical care.

PMID: 24875731 [PubMed - as supplied by publisher]

Cesk Slov Oftalmol. 2014 Spring;70(1):15-20.

[Microperimetry in the Wet Form of Age - Related Macular Degeneration (ARMD)].[Article in Czech]

Sokolová Šidlová J, Synek S, Zampachová E, Beneš P, Matúšová J.

Aim: Introduce and evaluate the microperimetry as a support technique in the evaluation of the ARMD wet form bevacizumab (Avastin) treatment efficacy.

Methods: Twenty-one patients (21 eyes) with ARMD wet form were included in the study; they were examined by means by OCT/SLO (optic coherence tomography / scanning laser ophthalmoscope) machine whose part is the microperimetric test. In each patient, there were two microperimetric examinations performed - the first one was done one day before the application of the treatment and the second one one month after the application. The values of retinal sensitivity and possible absolute scotomas were recorded by the microperimeter. The best-corrected visual acuity measurement was recorded as well.

Results: The measurements were performed in the group of 21 eyes of 8 men and 13 women (age 50 - 86 years). There were the differences between the genders evaluated (at the selected level of significance of

0.05) in the following categories: age, retinal sensitivity, absolute scotoma extent, and visual acuity. Differences among men and women were found in retinal sensitivity, before the treatment and after it as well. The influence of the gender we may exclude, except the category of retinal sensitivity. In the categories age, visual acuity, and even absolute scotoma extent, no differences between genders were found. The retinal sensitivity (in case of fixation up to 4 degrees) improved in the men group from 14.49 dB ± 2.44 dB to 15.65 dB ± 2.61 dB, in the women group from 10.47 dB ± 3.11 dB to 12.05 dB ± 3.10 dB. The visual acuity in the whole group (men + women) increased from 0.48 ± 0.17 to 0.60 ± 0.18, so improved by 12 %. Statistically significant is also the result of the treatment in the absolute scotoma.

Conclusion: Microperimetry is a suitable method to evaluate the function of macular region of the retina. The study confirms, that the treatment of wet form ARMD by means of intravitreal bevacizumab injections significantly increases the retinal sensitivity (in dB), decreases of the extent of absolute scotoma and improves the visual acuity by 12 %. Key words: microperimetry, ARMD, Avastine, retinal sensitivity, visual acuity, absolute scotoma.

PMID: 24862371 [PubMed - in process]

Arq Neuropsiquiatr. 2014 May;72(5):333-6.

Charles Bonnet syndrome: characteristics of its visual hallucinations and differential diagnosis.

Vale TC, Fernandes LC, Caramelli P.

Objective: To present an eight-case serie of patients with Charles Bonnet syndrome (CBS).

Method: All patients were initially evaluated by an ophthalmologist and then submitted to a neurologic evaluation with exclusion of alternative psychiatric and neurologic diagnoses.

Results: Five patients were male (62.5%) and the mean age was 52.3+16.0 years. Two patients suffered from severe myopia and glaucoma, three had retinitis pigmentosa, one had anterior ischemic optic neuropathy, one had age-related macular degeneration and one had toxoplasmic retinochoroiditis. Mean visual acuity in the right eye was 1,12 logMAR and in the left eye 0.57 logMAR. A mean delay of 41.7 months occurred until diagnosis. All hallucinations were complexes and mostly ocurred on a weekly-basis (62.5%) and lasted for seconds (87.5%).

Conclusions: Physicians who care for low vision patients should be aware of CBS and appropriately diagnose its hallucinations after exclusion of psychiatric and neurologic diseases.

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Pathogenesis

Autoimmune Dis. 2014;2014:532487. Epub 2014 Apr 30.

Potential Sources and Roles of Adaptive Immunity in Age-Related Macular Degeneration: Shall We Rename AMD into Autoimmune Macular Disease?

Camelo S.

Abstract: Age-related macular degeneration (AMD) is the leading cause of vision loss in the elderly throughout the industrialized world. Its most prominent pathologic features are lesions involving the retinal pigment epithelium (RPE) the Bruch's membrane, the degeneration of photoreceptors, and, in the most aggressive cases, choroidal neovascularization. Genetic associations between the risk of developing AMD and polymorphism within components of the complement system, as well as chemokine receptors expressed on microglial cells and macrophages, have linked retinal degeneration and choroidal

neovascularization to innate immunity (inflammation). In addition to inflammation, players of the adaptive immunity including cytokines, chemokines, antibodies, and T cells have been detected in animal models of AMD and in patients suffering from this pathology. These observations suggest that adaptive immunity might play a role in different processes associated with AMD such as RPE atrophy, neovascularization, and retinal degeneration. To this date however, the exact roles (if any) of autoantibodies and T cells in AMD remain unknown. In this review we discuss the potential effects of adaptive immune responses in AMD pathogenesis.

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Optom Vis Sci. 2014 May 29. [Epub ahead of print]

Melanopsin-Expressing Intrinsically Photosensitive Retinal Ganglion Cells in Retinal Disease.

Feigl B, Zele AJ.

Abstract: Melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs) are a class of photoreceptors with established roles in non-image-forming processes. Their contributions to image-forming vision may include the estimation of brightness. Animal models have been central for understanding the physiological mechanisms of ipRGC function and there is evidence of conservation of function across species. Intrinsically photosensitive retinal ganglion cells can be divided into five ganglion cell subtypes that show morphological and functional diversity. Research in humans has established that ipRGCs signal environmental irradiance to entrain the central body clock to the solar day for regulating circadian processes and sleep. In addition, ipRGCs mediate the pupil light reflex (PLR), making the PLR a readily accessible behavioral marker of ipRGC activity. Less is known about ipRGC function in retinal and optic nerve disease, with emerging research providing insight into their function in diabetes, retinitis pigmentosa, glaucoma, and hereditary optic neuropathy. We briefly review the anatomical distributions, projections, and basic physiological mechanisms of ipRGCs and their proposed and known functions in animals and humans with and without eye disease. We introduce a paradigm for differentiating inner and outer retinal inputs to the pupillary control pathway in retinal disease and apply this paradigm to patients with age-related macular degeneration (AMD). In these cases of patients with AMD, we provide the initial evidence that ipRGC function is altered and that the dysfunction is more pronounced in advanced disease. Our perspective is that with refined pupillometry paradigms, the PLR can be extended to AMD assessment as a tool for the measurement of inner and outer retinal dysfunction.

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PLoS One. 2014 May 29;9(5):e98275. doi: 10.1371/journal.pone.0098275. eCollection 2014.

Protection of Retina by αB Crystallin in Sodium Iodate Induced Retinal Degeneration.

Zhou P, Kannan R, Spee C, Sreekumar PG, Dou G, Hinton DR.

Abstract: Age-related macular degeneration (AMD) is a leading cause of blindness in the developed world. The retinal pigment epithelium (RPE) is a critical site of pathology in AMD and αB crystallin expression is increased in RPE and associated drusen in AMD. The purpose of this study was to investigate the role of αB crystallin in sodium iodate (NaIO3)-induced retinal degeneration, a model of AMD in which the primary site of pathology is the RPE. Dose dependent effects of intravenous NaIO3 (20-70 mg/kg) on development of retinal degeneration (fundus photography) and RPE and retinal neuronal loss (histology) were determined in wild type and αB crystallin knockout mice. Absence of αB crystallin augmented retinal degeneration in low dose (20 mg/kg) NaIO3-treated mice and increased retinal cell apoptosis which was mainly localized to the RPE layer. Generation of reactive oxygen species (ROS) was observed with NaIO3 in mouse and human RPE which increased further after αB crystallin knockout or siRNA knockdown,

respectively. NaIO3 upregulated AKT phosphorylation and peroxisome proliferator-activator receptor-γ (PPARγ) which was suppressed after αB crystallin siRNA knockdown. Further, PPARγ ligand inhibited NaIO3-induced ROS generation. Our data suggest that αB crystallin plays a critical role in protection of NaIO3-induced oxidative stress and retinal degeneration in part through upregulation of AKT phosphorylation and PPARγ expression.

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Epidemiology

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Lipids, Lipid Genes and Incident Age-Related Macular Degeneration: The Three Continent Age-Related Macular Degeneration Consortium.

Klein R, Myers CE, Buitendijk GH, Rochtchina E, Gao X, de Jong PT, Sivakumaran TA, Burlutsky G, McKean-Cowdin R, Hofman A, Iyengar SK, Lee KE, Stricker BH, Vingerling JR, Mitchell P, Klein BE, Klaver CC, Wang JJ.

PURPOSE: To describe associations of serum lipid levels and lipid pathway genes to the incidence of age-related macular degeneration (AMD).

DESIGN: Meta-analysis.

METHODS SETTING: Three population-based cohorts.

POPULATION: 6953 participants from the Beaver Dam Eye Study (BDES), Blue Mountains Eye Study (BMES) and Rotterdam Study (RS).

OBSERVATION PROCEDURES: Participants were followed over 20 years and examined at 5-year intervals. Hazard ratios (HRs) associated with lipid levels per standard deviation above the mean or associated with each additional risk allele for each lipid pathway gene were calculated using random-effects inverse-weighted meta-analysis models, adjusting for known AMD risk factors.

MAIN OUTCOME MEASURES: Incidence of AMD.

RESULTS: The average 5-year incidences of early AMD were 8.1%, 15.1%, and 13.0% in the BDES, BMES, and RS, respectively. Substantial heterogeneity in the effect of cholesterol and lipid pathway genes on the incidence and progression of AMD was evident when the data from the three studies were combined in meta-analysis. After correction for multiple comparisons, we did not find a statistically significant association between any of the cholesterol measures, statin use, or serum lipid genes and any of the AMD outcomes in the meta-analysis.

CONCLUSION: In a meta-analysis, there were no associations of cholesterol measures, history of statin use, or lipid pathway genes to the incidence and progression of AMD. These findings add to inconsistencies in earlier reports from our studies and others showing weak associations, no associations, or inverse associations of high-density lipoprotein cholesterol and total cholesterol with AMD.

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Optom Vis Sci. 2014 May 29. [Epub ahead of print]

Is Renal Function Associated with Early Age-Related Macular Degeneration?

Chong EW, Guymer RH, Klein R, Klein BE, Cotch MF, Wang JJ, Shlipak MG, Wong TY.

PURPOSE: Age-related macular degeneration (AMD) and chronic kidney disease both involve immune dysregulation and may share underlying pathophysiologic changes to systemic homeostasis. Hence, we aim to evaluate associations between impaired kidney function and early AMD, in a search for urinary biomarkers for AMD.

METHODS: A population-based, cross-sectional analysis of persons aged 45 to 84 years was conducted with renal function measured using serum creatinine and cystatin C levels and the estimated glomerular filtration rate (eGFR) calculated. Age-related macular degeneration status was ascertained from retinal photographs.

RESULTS: Of 5874 participants, 221 had early AMD. High serum cystatin C and low eGFR (≤60 ml/min/1.73 m) were not associated with early AMD in our multivariate analyses. Among normotensive persons, however, highest versus other deciles of cystatin C were associated with an increased prevalence of early AMD (odds ratio, 1.80; 95% confidence interval, 1.00 to 3.23).

CONCLUSIONS: Results could not confirm an association between kidney function and early AMD. The borderline association between cystatin C and early AMD in normotensive persons require further verification.

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Am J Ophthalmol. 2014 May 27. pii: S0002-9394(14)00294-3. doi: 10.1016/j.ajo.2014.05.023. [Epub ahead of print]

Visual Acuity and Subfoveal Choroidal Thickness. The Beijing Eye Study.

Shao L, Xu L, Wei WB, Chen CX, Du KF, Li XP, Yang M, Wang YX, You QS, Jonas JB.

PURPOSE: To examine the association between best corrected visual acuity (BCVA) and subfoveal choroidal thickness.

DESIGN: Population-based study.

METHODS: The Beijing Eye Study 2011 included 3468 subjects with an age of 50+ years. The participants underwent an ophthalmological examination including spectral-domain optical coherence tomography with enhanced depth imaging for measurement of choroidal thickness. BCVA was measured as logarithm of the minimal angle of resolution.

RESULTS: Out of the 3468 participants, choroidal measurements were available for 3233 (93.2%) subjects. In multivariate analysis, better BCVA was significantly associated with thicker subfoveal choroid (P<0.001) in general and a subfoveal choroid thicker than 30 µm (P<0.001) in particular, after adjusting for younger age (P<0.001), higher level of education (P<0.001), taller body stature (P<0.001), higher body mass index (P=0.005), absence of glaucoma (P=0.001), absence of diabetic retinopathy (P<0.001), absence of late stage of age-related macular degeneration (P<0.001), and axial length shorter than 26.0 mm (P<0.001) (correlation coefficient r:0.56). If eyes with glaucoma, diabetic retinopathy, late stage of age-related macular degeneration and myopic retinopathy were excluded, better BCVA was still significantly associated with thicker subfoveal choroid (P<0.001) and subfoveal choroid thicker than 30 µm (P<0.001) in multivariate analysis. In a reverse manner, thicker subfoveal choroid was associated with better BCVA (P<0.001), after adjusting for younger age (P<0.001), male gender (P<0.001), longer axial length (P<0.001), and higher corneal curvature radius (P<0.001).

CONCLUSIONS: Better visual acuity is strongly associated with thicker subfoveal choroid independently of additional factors such as age, axial length, educational level and major ocular diseases.

PMID: 24878308 [PubMed - as supplied by publisher]

Genetics

Sci Rep. 2014 May 28;4:5081. doi: 10.1038/srep05081.

Detecting a weak association by testing its multiple perturbations: a data mining approach.

Lo MT, Lee WC.

Abstract: Many risk factors/interventions in epidemiologic/biomedical studies are of minuscule effects. To detect such weak associations, one needs a study with a very large sample size (the number of subjects, n). The n of a study can be increased but unfortunately only to an extent. Here, we propose a novel method which hinges on increasing sample size in a different direction-the total number of variables (p). We construct a p-based 'multiple perturbation test', and conduct power calculations and computer simulations to show that it can achieve a very high power to detect weak associations when p can be made very large. As a demonstration, we apply the method to analyze a genome-wide association study on age-related macular degeneration and identify two novel genetic variants that are significantly associated with the disease. The p-based method may set a stage for a new paradigm of statistical tests.

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Ophthalmic Genet. 2014 May 27:1-5. [Epub ahead of print]

Genetic Variants in the SKIV2L Gene in Exudative Age-related Macular Degeneration in the Japanese Population.

Yoneyama S, Sakurada Y, Mabuchi F, Sugiyama A, Kubota T, Iijima H.

Abstract Background: To investigate whether genetic variant in superkiller viralicidic activity 2-like (SKIV2L) gene is associated with exudative age-related macular degeneration (AMD) including neovascular AMD, polypoidal choroidal vasculopathy (PCV), and retinal angiomatous proliferation (RAP).

Materials and Methods: A total of 517 patients with exudative AMD comprised of 157patients with neovascular AMD, 333 patients with PCV, and 27patients with RAP, and 205 controls were enrolled in this study. Rs429608 inSKIV2L, rs800292 in complement factor H (CFH), rs10490924 in age-related maculopathy susceptibility2 (ARMS2) gene was genotyped using TaqMan technology. Logistic regression analysis was performed to correlate the risk for exudative AMD with demographic and genetic factors.

Results: The A allele frequency of rs429608 in the SKIV2L gene was significantly higher in controls (13.9%) than in those with neovascular AMD (5.7%, p = 0.002), PCV (7.2%, p = 0.003) and RAP (3.7%, p = 0.0345). After adjusting for age, gender, ARMS2 A69S, and CFHI62V, the A allele of rs429608 was significantly protective against neovascular AMD (odds ratio [OR] 0.24, 95% confidence interval [CI] 0.122-0.484, p < 0.001), PCV (OR 0.43, 95% CI 0.262-0.704, p = 0.001), RAP (OR 0.09, 95% CI 0.014-0.581, p = 0.011).

Conclusions: A SKIV2L variant was associated with protection against exudative AMD regardless of subtypes in the Japanese population.

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Ophthalmic Genet. 2014 May 27:1-6. [Epub ahead of print]

Association of Specific Genetic Polymorphisms with Age-related Macular Degeneration in a Northern Chinese Population.

Zhuang W, Li H, Liu Y, Zhao J, Ha S, Xiang W, Bai X, Li Z, Han Y, Sheng X.

Abstract Purpose: The associations between genetic variants located in CFH, CFB, ARMS2 and HTRA1 and the risk of age-related macular degeneration (AMD) in a northern Chinese population were investigated.

Methods: A case-control association study of 150 AMD patients and 145 ethnicity- and gender-matched controls were recruited. Genomic DNA was prepared from peripheral blood after the participants underwent comprehensive eye examinations. All individuals were genotyped for eight single nucleotide polymorphisms (SNPs) in four specific genes. Genotypic distribution was tested for Hardy-Weinberg equilibrium. Statistical analysis was performed for genotype, allele and haplotype frequencies along with their p values and corresponding odds ratios (OR), 95% confidence intervals (95% CI) and measures of linkage disequilibrium (LD). Bonferroni corrections for multiple comparisons were performed.

Results: Among the SNPs genotyped, p values of seven SNPs were less than 0.05 in the genotypic distributions and allele frequencies between AMD and control subjects. However, after Bonferroni correction, the genotype and allele distributions of two SNPs in CFH (rs10737680, rs1410996), one SNP (rs10490924) in ARMS2 and one SNP (rs11200638) in HTRA1 differed significantly between the controls and AMD patients. Two SNPs were significantly associated with AMD in the allele distributions. They were rs800292 (pallele = 0.006, OR [CI] = 1.643[1.155-2.336]) in CFH and rs641153 (pallele = 0.002, OR [CI] = 0.273[0.120-0.620]) in CFB. Five haplotypes in CFH significantly predisposed patients to AMD after 50,000 permutations (p = 0.0099, p = 0.0099, p = 0.0013, p = 0.0414 and p = 0.0327).

Conclusions: Gene variants in CFH, ARMS2 and HTRA1 are related to an increased risk of AMD in a northern Chinese population.

PMID: 24865190 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2014 May 26. doi: 10.1111/aos.12433. [Epub ahead of print]

Flicker-induced retinal vasodilatation is not dependent on complement factor H polymorphism in healthy young subjects.

Told R, Palkovits S, Boltz A, Schmidl D, Napora KJ, Werkmeister RM, Haslacher H, Frantal S, Popa-Cherecheanu A, Schmetterer L, Garhöfer G.

PURPOSE: The complement factor H (CFH) tyrosine 402 histidine (Y402H, rs1061170) variant is known to be significantly associated with age-related macular degeneration (AMD). Whether this genetic variant may impact retinal blood flow regulation is largely unknown. This study investigated whether flicker-induced vasodilation, an indicator for the coupling between neural activity and blood flow, is altered in subjects carrying the rs1061170 risk allele.

METHODS: One hundred healthy subjects (aged between 18 and 45 years) were included in this study. Retinal blood flow regulation was tested by assessing retinal vessel calibres in response to stimulation with diffuse flicker light. Retinal vascular flicker responses were determined with a Dynamic Vessel Analyzer (DVA). In addition, genotyping for rs1061170 was performed.

RESULTS: Eighteen subjects were homozygous for the risk allele C, 50 were homozygous for the ancestral allele T, and 31 subjects were heterozygous (CT). One subject had to be excluded from data evaluation, as no genetic analysis could be performed due to technical difficulties. Baseline diameters of retinal arteries (p = 0.39) and veins (p = 0.64) were comparable between the three groups. Flicker-induced vasodilation in both retinal arteries (p = 0.38) and retinal veins (p = 0.62) was also comparable between the three studied groups.

CONCLUSIONS: Our data indicate that homozygous healthy young carriers of the C risk allele at rs1061170 do not show abnormal flicker-induced vasodilation in the retina. This suggests that the high-risk genetic variant of CFH polymorphism does not impact neuro-vascular coupling in healthy subjects.

PMID: 24863099 [PubMed - as supplied by publisher]

Expert Rev Ophthalmol. 2013 Apr 1;8(2):127-140.

Genetic risk, ethnic variations and pharmacogenetic biomarkers in age-related macular degeneration and polypoidal choroidal vasculopathy.

Kuo JZ, Wong TY, Ong FS.

PMID: 24860613 [PubMed] PMCID: PMC4029770

Diet & lifestyle

Optom Vis Sci. 2014 May 29. [Epub ahead of print]

Effects of Macular Degeneration and Ambient Light on Curb Negotiation.

Alexander MS, Lajoie K, Neima DR, Strath RA, Robinovitch SN, Marigold DS.

PURPOSE: To determine how age-related macular degeneration (AMD) and changes in ambient light affect the ability to negotiate a curb while walking.

METHODS: Ten older adults with AMD and 11 normal-sighted control subjects performed a curb negotiation task under normal light (~600 lux), dim light (~0.7 lux), and following a sudden reduction (~600 to 0.7 lux) of light. In this task, subjects walked and stepped up or down a simulated sidewalk curb. Movement kinematics and ground reaction forces were measured during curb ascent and descent. Habitual visual acuity, contrast sensitivity, and visual fields were also assessed.

RESULTS: Apart from slower gait speed in those with AMD, there were no differences between groups during curb ascent for any other measure. During curb descent, older adults with AMD frequently used shuffling steps in the approach phase to locate the curb edge and showed prolonged double support duration stepping over the curb compared with control subjects. However, reduced lighting, particularly a sudden reduction, led to several significant changes in movement characteristics in both groups. For instance, toe clearance stepping up the curb was greater, and landing force stepping down was reduced. In addition, slower gait speed and greater double support duration were evident in curb ascent and descent. In AMD subjects, contrast sensitivity, visual acuity, and visual field threshold were associated with several kinematic measures in the three light conditions during curb negotiation.

CONCLUSIONS: Minor AMD-specific changes in movement are seen during curb negotiation. However, attenuated lighting greatly impacts curb ascent and descent, regardless of eye disease, which manifests as a cautious walking strategy and may increase the risk of falling. Environmental enhancements that reduce the deleterious effects of poor lighting are required to improve mobility and quality of life of older adults, particularly those with AMD.

PMID: 24879086 [PubMed - as supplied by publisher]