Macular Disease Foundation AUSTRALIA
Our focus is your vision

MD Research News

Issue 162

Monday 6 January, 2014

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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

Graefes Arch Clin Exp Ophthalmol. 2013 Dec 24. [Epub ahead of print]

Clinical outcomes after switching treatment from intravitreal ranibizumab to aflibercept in neovascular age-related macular degeneration.

Heussen FM, Shao Q, Ouyang Y, Joussen AM, Müller B.

PURPOSE: To describe the treatment response to aflibercept in patients with exudative age-related macular degeneration that showed insufficient or diminishing treatment effects under ranibizumab.

METHODS: From December 2012 till June 2013 all patients receiving intravitreal injections of aflibercept after previous treatment with ranibizumab were collected in a database and retrospectively reviewed. Clinical data such as visual acuity or central subfield retinal thickness on optical coherence tomography (OCT) scans were analyzed for the time frame before, during, and shortly after the aflibercept injections. Of particular interest was the comparison of clinical features under ongoing ranibizumab treatment to the time during aflibercept treatment.

RESULTS: Seventy-one eyes of 65 patients were included in the study. All eyes had previous ranibizumab injections in their medical history, the average number of which was nine (range 3-43). For the total group the mean visual acuity (VA) before the first ranibizumab injection was 0.54 logMAR, and after the last ranibizumab injection was 0.57 logMAR. Mean VA changed from 0.47 logMAR before the first aflibercept injection to 0.25 logMAR after the last aflibercept injection. Central subfield retinal thickness (CSRT) on OCT changed from a mean of 417.28 µm to 349.52 µm under ranibizumab treatment and from 338.76 µm to 272.00 µm under aflibercept treatment. Interestingly, 33 % of cases that did not show a functional improvement under ranibizumab therapy gained visual acuity after aflibercept treatment.

CONCLUSION: Aflibercept appears to be an effective choice for patients with neovascular age-related macular degeneration who were resistant to previous therapy of ranibizumab. The longevity of this effect still remains questionable.

PMID: 24362854 [PubMed - as supplied by publisher]

Ophthalmologica. 2013 Dec 13. [Epub ahead of print]

Bimonthly Ranibizumab for Neovascular Age-Related Macular Degeneration.

Cohen SY, Maloberti B, Fajnkuchen F, Nghiem-Buffet S, Delahaye-Mazza C, Grenet T, Quentel G.

Background/Purpose: Recently, aflibercept was proposed with a protocol of a bimonthly fixed regimen. Our purpose was to evaluate the results of this regimen in patients treated with ranibizumab.

Method: We conducted a retrospective analysis of consecutive patients with naïve neovascular age-related macular degeneration treated with a bimonthly fixed regimen of intravitreal injections of ranibizumab after 3 monthly injections. Examination was performed every 4 weeks for 52 weeks, with the possibility of unscheduled rescue injections of ranibizumab.

Results: A total of 27 patients, 24 women and 3 men, aged from 68 to 90 years (mean: 81.2) were analyzed; 25 eyes (92.5%) lost <15 letters. Mean BCVA rose from 58.3 (range ± 12.9) to 66.7 (range ± 14.3) letters. The mean visual gain was 8.40 (range ± 13.2) letters; 11 patients (40.7%) gained ≥15 letters. The mean number of injections of ranibizumab was 8.77.

Conclusion: Bimonthly intravitreal ranibizumab achieved satisfactory visual results. However, patients who required additional injections did not experience significant visual gain.

PMID: 24356074 [PubMed - as supplied by publisher]

Surv Ophthalmol. 2014 Jan-Feb;59(1):1-18. doi: 10.1016/j.survophthal.2013.03.009.

Predictors of anti-VEGF treatment response in neovascular age-related macular degeneration.

Finger RP1, Wickremasinghe SS2, Baird PN2, Guymer RH2.

Abstract: Currently available evidence on predictors of anti-vascular endothelial growth factor (VEGF) treatment response in neovascular age-related macular degeneration was reviewed. No meta-analysis of results is possible because of a lack of controlled and randomized trials, varying treatment regimes and outcome measures used, as well as suboptimal reporting. For genetic factors, most evidence to date has been generated for single nucleotide polymorphisms (SNPs) in the complement factor H (CFH), and VEGF-A genes. Just under half of the SNPs assessed in the CFH gene and 15% of the SNPs assessed in the VEGF gene were found to be associated with visual outcomes or the number of injections required during follow-up. Some evidence suggests association of worse treatment outcomes as well as a younger age at treatment onset with an increasing number of risk alleles in known risk genes (CFH and ARMS2/HTRA1) and polymorphisms in the VEGF-A gene. Clinical factors such as higher age, a better visual acuity (VA), a larger choroidal neovascularization (CNV) lesion at baseline, and a delay between symptom onset and initiation of treatment of more than 3 weeks also impact outcomes. Conversely, a worse acuity at baseline predicted more gain in vision. Overall, patients presenting with good acuity at baseline were more likely to have good VA at follow up, but the gain afforded by treatment was impacted by a ceiling effect. Most available evidence suggests a strong association of clinical factors such as age, baseline VA, and CNV lesion size with anti-VEGF treatment outcomes. No behavioral factors such as smoking influence treatment outcomes. Based on the studies conducted so far, the evidence suggests that underlying genotype of known AMD risk associated genes or of the VEGF-A gene have a limited effect, whereas presenting clinical factors appear to be more important in determining treatment outcomes.

PMID: 24332379 [PubMed - in process]

Retina. 2014 Jan;34(1):18-23. doi: 10.1097/IAE.0000000000000008.

ENDOPHTHALMITIS ASSOCIATED WITH INTRAVITREAL INJECTIONS: Office-Based Setting and Operating Room Setting.

Tabandeh H, Boscia F, Sborgia A, Ciracì L, Dayani P, Mariotti C, Furino C, Flynn HW Jr.

PURPOSE: To report on the occurrence of endophthalmitis after intravitreal injections (IVI) in two different

settings: office-based and operating room.

METHODS: Consecutive case series. Retrospective review of all patients who underwent IVI by 2 physicians between January 2009 and December 2011. Group A underwent IVI in the examination room in office-based setting and Group B underwent IVI in the operating room.

RESULTS: A total of 11,710 IVIs were performed during the study period. Group A: A total of 8,647 IVIs performed including 2,041 ranibizumab, 6,169 bevacizumab, and 437 triamcinolone acetonide. The diagnosis included neovascular age-related macular degeneration (5,376), diabetic macular edema (1,587), retinal vein occlusion (1,068), and miscellaneous diagnosis (616). Group B: A total of 3,063 IVIs performed including 683 ranibizumab, 2,364 bevacizumab, and 16 triamcinolone acetonide. The diagnosis included neovascular age-related macular degeneration (1,836), diabetic macular edema (771), retinal vein occlusion (189), and miscellaneous diagnosis (267). A total of 5 cases (0.043%) of clinically suspected endophthalmitis occurred in 11,710 injections. Three cases (0.035%) occurred in Group A, and 2 cases (0.065%) occurred in Group B.

CONCLUSION: The rate of clinically suspected endophthalmitis after IVIs is low whether the procedure is performed in the office or operating room setting. The findings have implications in terms of the patient convenience, efficiency, and cost of administrating these treatments.

PMID: 24362413 [PubMed - in process]

BMC Ophthalmol. 2013 Dec 20;13:84. doi: 10.1186/1471-2415-13-84.

Risk factors of a reduced response to ranibizumab treatment for neovascular age-related macular degeneration - evaluation in a clinical setting.

Korb C, Zwiener I, Lorenz K, Mirshahi A, Pfeiffer N, Stoffelns B.

BACKGROUND: To identify risk factors for being a "reduced responder" to ranibizumab treatment in a clinical setting in patients with neovascular age-related macular degeneration.

METHODS: This retrospective study included 165 eyes of 165 consecutive patients with choroidal neovascularisation secondary to neovascular, age-related macular degeneration. Eyes were treated with three intravitreal injections of ranibizumab, followed by PRN (pro re nata) dosing thereafter. All patients were reevaluated every four weeks and then followed for six months. Reduced responders were defined as patients with a loss in visual acuity of at least 1 visual acuity line at the last follow-up and/or persistent intraretinal or subretinal fluid or detectable choroidal neovascularisation at the last follow-up, compared to baseline.

RESULTS: Overall, 58 out of 165 eyes (35.2%) were considered to be reduced responders to treatment at the end of follow-up. The initial CNV size at baseline was correlated with the risk of being a reduced responder at the end of follow-up ($p = 0.017$).

CONCLUSION: We identified the initial lesion size as a predictor for a reduced response to treatment in this study. Patients with a large initial lesion size should be thoroughly informed about the possible poorer response to the intravitreal treatment.

PMID: 24359591 [PubMed - in process]

World J Diabetes. 2013 Dec 15;4(6):310-318.

Ranibizumab in diabetic macular edema.

Krispel C, Rodrigues M, Xin X, Sodhi A.

Abstract: By 2050 the prevalence of diabetes will more than triple globally, dramatically increasing the societal and financial burden of this disease worldwide. As a consequence of this growth, it is anticipated that there will be a concurrent rise in the numbers of patients with diabetic macular edema (DME), already among the most common causes of severe vision loss worldwide. Recent available therapies for DME target the secreted cytokine, vascular endothelial growth factor (VEGF). This review focuses on the treatment of DME using the first humanized monoclonal antibody targeting VEGF that has been Food and Drug Administration-approved for the use in the eye, ranibizumab (Lucentis®).

PMID: 24379922 [PubMed - as supplied by publisher] PMCID: PMC3874491

World J Diabetes. 2013 Dec 15;4(6):303-309.

Vascular endothelial growth factor trap-eye (Aflibercept) for the management of diabetic macular edema.

Moradi A, Sepah YJ, Sadiq MA, Nasir H, Kherani S, Sophie R, Do DV, Nguyen QD.

Abstract: Diabetic retinopathy (DR) is the most common cause of visual loss among working age individuals. Diabetic macular edema (DME) is an important complication of DR that affects around one third of the patients with DR. Several treatments have been approved for DME ranging from blood pressure and glycemic control to photocoagulation and more recently the use of vascular endothelial growth factor (VEGF) antagonists. The index review discusses aflibercept (EYLEA®-Regeneron Pharmaceuticals, Inc., Tarrytown, New York, NY, and Bayer Healthcare Pharmaceuticals, Berlin, Germany) in the context of other VEGF antagonists currently available for the treatment of DME. A systematic search of literature was conducted on PubMed, Scopus, and Google Scholar with no limitation on language or year of publication. Pre-clinical studies of aflibercept have shown a higher affinity of this molecule for vascular endothelial growth factor A (VEGF-A) along with a longer duration of action as compared to other VEGF antagonists. Recent clinical trials have shown visual outcome results for aflibercept to be similarly favorable as compared to other available agents with the added benefit of fewer required injections and less frequent monitoring. Aflibercept presents a potential exciting new addition to the armamentarium of current VEGF antagonists available for the treatment of DME and other retinal vascular diseases. However, further studies are indicated to confirm the role, safety, and efficacy of aflibercept for DME.

PMID: 24379921 [PubMed - as supplied by publisher] PMCID: PMC3874490

World J Diabetes. 2013 Dec 15;4(6):231-3. doi: 10.4239/wjd.v4.i6.231.

Diabetic macular edema: Current management 2013.

Arevalo JF.

Abstract: Diabetic retinopathy (DR) is the leading cause of vision loss of working-age adults, and diabetic macular edema (DME) is the most frequent cause of vision loss related to diabetes. The Wisconsin Epidemiologic Study of Diabetic Retinopathy found the 14-year incidence of DME in type 1 diabetics to be 26%. Similarly the Diabetes Control and Complications Trial reported that 27% of type 1 diabetic patients develop DME within 9 years of onset. The most common type of diabetes, type 2, is strongly associated with obesity and a sedentary lifestyle. An even higher incidence of macular edema has been reported in older patients with type 2 diabetes. Within the last 5 years, the use of intravitreal corticosteroids and intravitreal anti-vascular endothelial growth factor (VEGF) agents have come into clinical practice for the management of DME and several recent randomized clinical trials have shown improved effectiveness of ranibizumab compared to focal/grid laser. In this theme issue, we discuss the classification of DR and the treatment options currently available for the treatment of DME including corticosteroids, anti-VEGF agents, combined therapy, enzymatic vitrectomy (vitreolysis), and new therapies.

PMID: 24379911 [PubMed] PMCID: PMC3874480

Case Rep Ophthalmol Med. 2013;2013:817186. doi: 10.1155/2013/817186. Epub 2013 Dec 9.

Bilateral intravitreal ranibizumab injection and panretinal photocoagulation in a 16-year-old girl with severe vaso-occlusive lupus retinopathy.

Doruk HC1, Cetin P2, Onen F2, Saatci AO1.

Abstract: A 16-year-old girl with fever of unknown origin and bilateral vaso-occlusive retinopathy with retinal neovascularization, preretinal hemorrhage, and serous macular detachment was treated with single bilateral 0.5 mg intravitreal ranibizumab injection prior to aggressive PRP with success. No systemic steroids or immunosuppressive therapy was employed at that time. She received the diagnosis of "systemic lupus erythematosus" five years after this episode with further systemic symptoms. In certain cases with vaso-occlusive type of lupus retinopathy, anti-VEGF agents may be administered in addition to panretinal photocoagulation to achieve better visual and anatomic outcome.

PMID: 24383026 [PubMed]

Am J Ophthalmol. 2013 Oct 19. pii: S0002-9394(13)00684-3. doi: 10.1016/j.ajo.2013.10.003. [Epub ahead of print]

Conjunctival Flora Antibiotic Resistance Patterns After Serial Intravitreal Injections Without Postinjection Topical Antibiotics.

Hsu J1, Gerstenblith AT2, Garg SJ2, Vander JF2.

PURPOSE: To report conjunctival bacterial flora antibiotic resistance patterns after serial intravitreal injections performed using a povidone-iodine preparation without the use of preinjection or postinjection topical antibiotics.

DESIGN: Prospective, interventional case series.

METHODS: Setting: Single-center clinical practice in Pennsylvania. Study Population: Thirteen eyes of 13 treatment-naïve patients undergoing serial intravitreal anti-vascular endothelial growth factor (VEGF) injections for exudative age-related macular degeneration or macular edema attributable to retinal vein occlusion. Intervention: Conjunctival cultures from the treatment eye were performed prior to each injection preparation. A minimum of 3 monthly conjunctival cultures were obtained per eye over the course of the study. Ocular surface preparation consisted of topical anesthetic and povidone-iodine 5% without the use of preinjection or postinjection topical antibiotics. Main Outcome Measures: Conjunctival flora growth patterns and antibiotic resistance patterns to several common antibiotics tested over the course of the study.

RESULTS: A total of 48 cultures were performed with a 77% culture positivity rate. Over the course of the serial conjunctival cultures in each patient, there was no evidence for emergence of resistant bacteria to any of the tested antibiotics (including fluoroquinolones and azithromycin) or significant alteration from baseline conjunctival flora. Of the 47 bacterial isolates, the most commonly isolated organism was coagulase-negative Staphylococcus both at baseline (73%) and following serial intravitreal injections (78%, P = .73).

CONCLUSIONS: Ocular surface preparation for intravitreal injection using povidone-iodine 5% alone in the absence of postinjection topical antibiotics does not appear to promote bacterial resistance or a discernible change in conjunctival flora.

PMID: 24332373 [PubMed - as supplied by publisher]

Mol Vis. 2013 Dec 20;19:2571-8.

The effect of CFH polymorphisms on the response to the treatment of age-related macular degeneration (AMD) with intravitreal ranibizumab.

Dikmetas O, Kadayıfcılar S, Eldem B.

PURPOSE: The purpose of this study is to evaluate the effect of complement factor H (CFH) Y402H CC and TT polymorphisms on treatment response to intravitreal ranibizumab injection in patients with wet age-related macular degeneration (AMD).

METHODS: One hundred ninety-three patients with choroidal neovascularization (CNV) secondary to AMD who were monitored for at least 6 months of follow-up, and with at least three ranibizumab injections, were included in the study. At the final examination, an increase in visual acuity (VA) of five letters or more compared to the initial VA was regarded as a good response, and a decrease in VA of five letters or more compared to the initial VA was evaluated as a poor response. A genetic examination was performed with a PCR melting curve analysis. In the statistical evaluation, SPSS version 18 software was used.

RESULTS: The mean age of the patients was 71.01 (55-86) years, the mean follow-up was 13.34 (6-36) months, and the mean number of injections was 4.02 (3-15). There were 96 patients in the good response group (Group 1) and 97 patients in the poor response group (Group 2). The initial VA in Group 1 was 41.34 (10-64) letters, the initial central macular thickness (CMT) was 213.40 (126-494) µm, and the initial lesion width was 3760 (1430-6430) µm. The initial VA in Group 2 was 52.89 (26-82) letters, the initial CMT was 257.60 (115-882) µm, and the initial lesion width was 4460 (1000-7650) µm. There was no statistically significant difference between the two groups in terms of the initial VA and CMT (p=0.094, p=0.083). However, there was a statistically significant difference between the groups in the width of the initial lesion (p=0.003). In Group 1, 15 CC, 30 TT, and 51 TC alleles were found, and in Group 2, 49 CC, two TT, and 46 TC alleles were found, and the distribution was significantly different between the two groups (p=0.012). The change in the distribution of genotypes was not associated with either the lesion size or VA (p=0.841). Fibrosis developed in 12 patients who were all poor responders.

CONCLUSIONS: CFH Y402H CC accompanied a poor response, and TT accompanied a good response in this series of patients with AMD undergoing ranibizumab therapy.

PMID: 24367156 [PubMed - in process] PMCID: PMC3869644

Ophthalmology. 2013 Dec 20. pii: S0161-6420(13)01056-7. doi: 10.1016/j.ophtha.2013.10.047. [Epub ahead of print]

Polymorphisms in Vascular Endothelial Growth Factor Receptor 2 Are Associated with Better Response Rates to Ranibizumab Treatment in Age-related Macular Degeneration.

Hermann MM1, van Asten F2, Muether PS1, Smailhodzic D2, Lichtner P3, Hoyng CB2, Kirchhof B1, Grefkes C4, den Hollander AI5, Fauser S6.

PURPOSE: Intravitreal anti-vascular endothelial growth factor (VEGF) injections are currently the standard treatment for neovascular age-related macular degeneration (AMD), but a broad range of response rates has been observed. We evaluated the association of single nucleotide polymorphisms (SNPs) in VEGF genes and their receptors (VEGFR) with the response rate to ranibizumab in 366 patients with neovascular AMD.

DESIGN: Case series study.

PARTICIPANTS: A total of 366 eyes of 366 patients with neovascular AMD.

METHODS: Visual acuity (VA) was determined at baseline, after 3 monthly ranibizumab injections, and

after 1 year of treatment. Genotyping of 126 SNPs in the genes encoding VEGF family members VEGFA, VEGFB, VEGFC, VEGFD (FIGF), and placental growth factor (PGF); VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4); and the gene encoding pigment epithelium-derived factor (PEDF) (SERPINF1) was performed.

MAIN OUTCOME MEASURES: The changes in VA after 3 injections and after 1 year of treatment and their association with VEGF and VEGFR genotypes.

RESULTS: Univariate analyses of variance (ANOVAs) revealed a significant effect of SNP rs4576072 in the VEGFR2 gene on VA change after 12 months ($F[1,235] = 14.05$; $P = 0.02$). A stepwise linear regression analysis returned a model ($P = 0.01$) with SNPs rs4576072 and rs6828477 in the VEGFR2 gene as independent predictors for VA change after 12 months, with a mean increase in VA of 0.26 on the logarithm of the minimum angle of resolution (logMAR) scale in patients with 3 contributing minor alleles compared with a loss of 0.03 logMAR in patients with no minor allele.

CONCLUSIONS: Polymorphisms in the VEGFR2/KDR gene significantly influence visual outcome in patients receiving ranibizumab treatment for neovascular AMD. This study shows that genetic variation partially explains the wide range of response to ranibizumab treatment, which in the future might help clinicians tailoring medical interventions to individual needs.

PMID: 24365177 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2013;7:2257-60. doi: 10.2147/OPTH.S55076. Epub 2013 Nov 27.

Diabetic papillopathy with macular edema treated with intravitreal ranibizumab.

Kim M, Lee JH, Lee SJ.

Abstract: We report a case of diabetic papillopathy that demonstrated a resolution of optic disk swelling and rapid visual recovery when intravitreal ranibizumab was administered. A 51-year-old male presented with acute painless visual loss in his right eye. His vision was 20/320 in the right eye and 20/50 in the left eye. Fundus examination of the right eye showed nonproliferative diabetic retinopathy with macular edema and a swollen optic disk. Fluorescein angiography showed dye leakage from the right optic disk. Optical coherent tomography revealed a significant increase in retinal nerve fiber-layer thickness. Magnetic resonance imaging of the brain was normal. The patient received a single intravitreal ranibizumab (0.5 mg) injection. Two weeks following injection, there was marked regression of the disk swelling and improvement of macular edema, with vision improving to 20/100. Three months following injection, there was complete resolution of the optic disk swelling. No further treatment was required.

PMID: 24348012 [PubMed] PMCID: PMC3848928

J Pharmacol Pharmacother. 2013 Dec;4(Suppl1):S38-S42.

Anti-vascular endothelial growth factor drugs safety and efficacy in ophthalmic diseases.

Ventrice P1, Leporini C1, Aloe JF2, Greco E3, Leuzzi G1, Marrazzo G1, Scorcia GB4, Bruzzichesi D4, Nicola V4, Scorcia V4.

Abstract: Macular degeneration is the leading cause of blindness in developed countries. In the treatment of neovascular age-related macular degeneration, vascular endothelial growth factor (VEGF) has emerged as a key target for therapy. The intravitreal injection of anti-VEGF drugs has been widely employed to reduce the disease progression and improve the visual outcomes of the affected patients. However, each intravitreal inoculation poses a risk of several complications as infection, inflammation, endophthalmitis, intraocular inflammation, increase of intraocular pressure and vitreous hemorrhage. This short review

evaluates the efficacy and the incidence of adverse drug reactions related to intravitreal administration of the main anti-VEGF drugs actually available: Bevacizumab, ranibizumab and aflibercept.

PMID: 24347979 [PubMed - as supplied by publisher] PMCID: PMC3853666

PLoS One. 2013 Dec 23;8(12):e82454. doi: 10.1371/journal.pone.0082454.

A meta-analysis of anti-vascular endothelial growth factor remedy for macular edema secondary to central retinal vein occlusion.

Huang P1, Niu W2, Ni Z3, Wang R3, Sun X4.

BACKGROUND: Central retinal vein occlusion (CRVO) associates with severe vision outcome and no proven beneficial treatment. Our meta-analysis intended to appraise the efficacy and safety of anti-vascular endothelial growth factor (anti-VEGF) agents in macular edema (ME) following CRVO.

METHODS: Data were collected and analyzed by Review Manager 5.2.1. We employed a random-effects model to eliminate between-study heterogeneity. Nfs (called fail-safe number) was calculated to evaluate the publication bias.

RESULTS: We included 5 trials consisting 323 cases and 281 controls. Primary outcomes showed that overall comparison of anti-VEGF agents with placebo control yielded a 374% and 136% increased tendency for a gain of 15 letters or more on Early Treatment Diabetic Retinopathy Study (ETDRS) chart (95% confidence interval [95% CI]: 2.43-9.23; P<0.00001; I(2) =59%, 95% CI: 1.60-3.49; P<0.0001; I(2) = 0%, respectively) at 6 and 12 months. Secondary outcomes showed that a 90% and 77% decreased risk at 6 and 12 months for a loss of 15 letters or more. The overall mean difference showed a statistically significance in best-corrected visual acuity (BCVA) on each time point. However, changes of central retinal thickness (CRT) lost significance at 12 months after 6-month as-needed treatment. The incidence of adverse events (AEs) had no statistical difference between anti-VEGF and placebo groups. Subgroup analyses indicated that patients receiving Aflibercept got the highest tendency to gain 15 letters or more (OR=9.78; 95% CI: 4.43-21.56; P<0.00001). Age controlled analysis suggested a weaken tendency of BCVA improvement in age over 50 (MD=12.26; 95% CI: 7.55-16.98; P<0.00001). Subgroup analysis by clinical classification showed a strengthen difference of BCVA changes at 6 months in ischemic type (MD= 19.65 letters, 95% CI: 13.15 to 26.14 letters, P<0.00001).

CONCLUSIONS: Our results showed that anti-VEGF agents were superior to placebo in CRVO-ME treatment with no statistically significant AEs, especially in younger people and for ischemic type.

PMID: 24376538 [PubMed - in process] PMCID: PMC3871640

Ophthalmology. 2013 Dec 13. pii: S0161-6420(13)01062-2. doi: 10.1016/j.ophtha.2013.11.004. [Epub ahead of print]

Intravitreal Anti-Vascular Endothelial Growth Factor for Submacular Hemorrhage from Choroidal Neovascularization.

Kim JH1, Chang YS2, Kim JW2, Kim CG2, Yoo SJ2, Cho HJ2.

PURPOSE: To evaluate the efficacy of intravitreal anti-vascular endothelial growth factor (VEGF) monotherapy for patients diagnosed with exudative age-related macular degeneration (AMD) accompanied by submacular hemorrhage.

DESIGN: Retrospective, observational case series.

PARTICIPANTS: Ninety-one eyes of 91 patients who initially presented with submacular hemorrhage

associated with exudative AMD from October 2009 to September 2012. Patients were followed up for at least 6 months after treatment.

METHODS: Best-corrected visual acuity (BCVA) was measured at diagnosis and at 1, 3, and 6 months after treatment. The duration of symptoms was estimated. The extent of hemorrhage was estimated using fundus photography, and central foveal thickness was measured using optical coherence tomography. Change in BCVA during 6 months after treatment was estimated. The correlation of BCVA at 6 months with duration of symptoms, extent of hemorrhage, and central foveal thickness was evaluated.

MAIN OUTCOME MEASURES: The BCVA, duration of symptoms, extent of hemorrhage, and central foveal thickness.

RESULTS: The mean duration of symptoms was 27.6±39.5 days. The mean extent of hemorrhage was 7.8±5.6 disc areas, and the mean central foveal thickness was 610.1±249.6 μm. All eyes were treated with 3.2±0.8 (range, 1-5) monthly intravitreal anti-VEGF injections during the 6-month follow-up period. The logarithm of the minimum angle of resolution BCVA at diagnosis and at 1, 3, and 6 months after the initial diagnosis was 1.38±0.53 (Snellen equivalent, 20/479), 1.27±0.57, 1.05±0.58, and 0.96±0.65 (Snellen equivalent, 20/182), respectively. The BCVA at 6 months significantly improved from baseline ($P < 0.001$). Poor BCVA at 6 months correlated with a longer duration of symptoms, greater extent of hemorrhage, and greater central foveal thickness ($P = 0.008$, $P = 0.004$, and $P = 0.014$, respectively).

CONCLUSIONS: Anti-VEGF monotherapy was found to be a useful treatment option for exudative AMD accompanied by submacular hemorrhage. However, the limited efficacy in eyes with large hemorrhage may suggest the need for more aggressive treatment in these cases.

PMID: 24342019 [PubMed - as supplied by publisher]

Middle East Afr J Ophthalmol. 2013 Oct;20(4):315-20. doi: 10.4103/0974-9233.120014.

Combined therapy for diabetic macular edema.

Al Rashaed S, Arevalo JF.

Abstract: Diabetic macular edema (DME) is the main cause of visual impairment in diabetic patients. Macular edema within 1 disk diameter of the fovea is present in 9% of the diabetic population. The management of DME is complex and often multiple treatment approaches are needed. This review demonstrates the benefits of intravitreal triamcinolone, bevacizumab and ranibizumab as adjunctive therapy to macular laser treatment in DME. The published results indicate that intravitreal injections of these agents may have a beneficial effect on macular thickness and visual acuity, independent of the type of macular edema that is present. Therefore, pharmacotherapy could complement focal/grid laser photocoagulation in the management of DME. For this review, we performed a literature search and summarized recent findings regarding combined therapy for DME.

PMID: 24339681 [PubMed - in process] PMCID: PMC3841949

Other treatment & diagnosis

Ophthalmic Surg Lasers Imaging Retina. 2013 Dec 25:1-14. doi: 10.3928/23258160-20131217-01. [Epub ahead of print]

Change in Drusen Volume as a Novel Clinical Trial Endpoint for the Study of Complement Inhibition in Age-related Macular Degeneration.

de Amorim Garcia Filho CA, Yehoshua Z, Gregori G, Nunes RP, Penha FM, Moshfeghi AA, Zhang K,

Feuer W, Rosenfeld PJ.

BACKGROUND AND OBJECTIVE: To evaluate the change in drusen volume following treatment with eculizumab, a systemic inhibitor of complement component 5.

PATIENTS AND METHODS: Single-center, prospective, randomized, double-masked clinical trial. Patients were randomized 2:1 to receive intravenous eculizumab or placebo over 26 weeks. Main outcome measure: decrease in drusen volume of at least 50% at 26-week follow-up.

RESULTS: Mean drusen cube root volumes were 0.49 mm and 0.47 mm (P = .64) at baseline and 0.51 mm and 0.42 mm (P = .17) at 26 weeks in the eculizumab and placebo groups, respectively. In the placebo group, one eye had a decrease in drusen volume of at least 50% and two eyes developed neovascularization through 26 weeks.

CONCLUSION: Systemic complement inhibition with eculizumab did not significantly reduce drusen volume. Drusen growth was dependent on the number of complement at-risk alleles. Future trials should consider the use of a composite clinical trial endpoint in which efficacy is defined by the treatment's ability to prevent drusen growth, neovascularization, and the formation of geographic atrophy over 1 year. [Ophthalmic Surg Lasers Imaging Retina. 2014;45:xxx-xxx.].

PMID: 24354307 [PubMed - as supplied by publisher]

Nihon Ganka Gakkai Zasshi. 2013 Oct;117(10):799-807.

[Clinical findings and macular lesions in basal laminar drusen].[Article in Japanese]

Takeda M1, Sato Y2, Ogino T3, Imaizumi H4, Okushiba U4.

PURPOSE: To investigate the clinical characteristics and accompanying macular lesions in Japanese patients with basal laminar drusen (BLD).

DESIGN: Retrospective cross-sectional study. PATIENTS and

METHODS: Fifty four eyes of 27 Japanese patients with BLD were examined for the clinical characteristics of BLD and accompanying macular lesions using retro-mode imaging (Scanning Laser Ophthalmoscope F-10, Nidek) in addition to current methods such as fluorescein angiography (FA), indocyanine green angiography (IA), fundus autofluorescence (FAF) and spectral domain optical coherence tomography (SD-OCT).

RESULTS: 1)BLD was more clearly identified using retro-mode imaging than any of the other current imaging methods, and was divided into two types: a crater type (relatively sparsely distributed BLD with many soft drusens) and a mesh type (uniformly distributed BLD). 2) BLD in both eyes was more common in female patients, and had the same type, distribution and similar macular lesions in both eyes. 3) Among the macular lesions, we observed macular atrophy, retinal angiomatous proliferation and vitelliform detachment in many patients, in contrast to few cases of choroidal neovascularization and no polypoidal choroidal vasculopathy.

CONCLUSIONS: BLD may be regarded as a disease that is different from age-related macular degeneration (AMD).

PMID: 24354264 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2013 Dec 17. pii: iovs.13-13034v1. doi: 10.1167/iovs.13-13034. [Epub ahead of print]

Reduced Fluorescein Angiography and Fundus Photography Use in the Management of

Neovascular Macular Degeneration and Macular Edema over the Past Decade.

Schneider EW, Mruthyunjaya P, Talwar N, Harris Nwanyanwu K, Nan B, Stein JD.

Purpose: To assess recent trends in the use of diagnostic testing for neovascular age-related macular degeneration (NVAMD) and macular edema (ME).

Methods: Claims data from a managed-care network were analyzed on patients with NVAMD (n=22,954) or ME (n=31,810) to assess the use of fluorescein angiography (FA), fundus photography (FP), and optical coherence tomography (OCT) from 2001 to 2009. Repeated-measures logistic regression was performed to compare patients' odds of undergoing these procedures in 2001, 2005, and 2009. In addition, the proportions of patients with an incident NVAMD or ME diagnosis in 2003 or 2008 who underwent FA, FP, and OCT were compared.

Results: From 2001 to 2009 among patients with NVAMD, the odds of undergoing OCT increased 23-fold, whereas the odds of receiving FA and FP decreased by 68% and 79%, respectively. Similar trends were observed for ME. From 2003 to 2008, the proportion of patients undergoing OCT within 1 year of initial diagnosis increased by 315% for NVAMD and by 143% for ME; the proportion undergoing OCT without FA within 1 year increased by 463% for NVAMD and by 216% for ME.

Conclusion: Use of OCT increased dramatically over the past decade, whereas use of FA and FP declined considerably, suggesting that OCT may be replacing more traditional diagnostic testing in patients with NVAMD or ME. Future studies should evaluate whether this increased reliance on OCT instead of FA and FP affects patient outcomes.

PMID: 24346174 [PubMed - as supplied by publisher]

Transl Vis Sci Technol. 2013 Nov;2(7):7. Epub 2013 Dec 23.

Reading Center Characterization of Central Retinal Vein Occlusion Using Optical Coherence Tomography During the COPERNICUS Trial.

Decroos FC1, Stinnett SS2, Heydary CS2, Burns RE2, Jaffe GJ2.

PURPOSE: To determine the impact of segmentation error correction and precision of standardized grading of time domain optical coherence tomography (OCT) scans obtained during an interventional study for macular edema secondary to central retinal vein occlusion (CRVO).

METHODS: A reading center team of two readers and a senior reader evaluated 1199 OCT scans. Manual segmentation error correction (SEC) was performed. The frequency of SEC, resulting change in central retinal thickness after SEC, and reproducibility of SEC were quantified. Optical coherence tomography characteristics associated with the need for SECs were determined. Reading center teams graded all scans, and the reproducibility of this evaluation for scan quality at the fovea and cystoid macular edema was determined on 97 scans.

RESULTS: Segmentation errors were observed in 360 (30.0%) scans, of which 312 were interpretable. On these 312 scans, the mean machine-generated central subfield thickness (CST) was 507.4 ± 208.5 μm compared to 583.0 ± 266.2 μm after SEC. Segmentation error correction resulted in a mean absolute CST correction of 81.3 ± 162.0 μm from baseline uncorrected CST. Segmentation error correction was highly reproducible (intraclass correlation coefficient [ICC] = 0.99-1.00). Epiretinal membrane (odds ratio [OR] = 2.3, $P < 0.0001$), subretinal fluid (OR = 2.1, $P = 0.0005$), and increasing CST (OR = 1.6 per 100-μm increase, $P < 0.001$) were associated with need for SEC. Reading center teams reproducibly graded scan quality at the fovea (87% agreement, kappa = 0.64, 95% confidence interval [CI] 0.45-0.82) and cystoid macular edema (92% agreement, kappa = 0.84, 95% CI 0.74-0.94).

CONCLUSIONS: Optical coherence tomography images obtained during an interventional CRVO treatment

trial can be reproducibly graded. Segmentation errors can cause clinically meaningful deviation in central retinal thickness measurements; however, these errors can be corrected reproducibly in a reading center setting.

TRANSLATIONAL RELEVANCE: Segmentation errors are common on these images, can cause clinically meaningful errors in central retinal thickness measurement, and can be corrected reproducibly in a reading center setting.

PMID: 24381819 [PubMed] PMCID: PMC3876727

Arch Soc Esp Oftalmol. 2013 Dec 11. pii: S0365-6691(13)00377-8. doi: 10.1016/j.oftal.2013.10.010. [Epub ahead of print]

Vitreomacular traction in patients with exudative age-related macular degeneration. [Article in English, Spanish]

Abreu González R1, Gallego-Pinazo R2, Pérez Muñoz D2, Pascual-Camps CI3, Pérez Méndez L4.

PMID: 24332686 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Dec 11. pii: S0161-6420(13)01071-3. doi: 10.1016/j.ophtha.2013.11.009. [Epub ahead of print]

Emerging Therapies for Neovascular Age-related Macular Degeneration: The Therapeutic Potential of Intravenous Immunoglobulin.

Shin JI1, Bayry J2.

PMID: 24332538 [PubMed - as supplied by publisher]

J Lipid Res. 2013 Dec 23. [Epub ahead of print]

Spatial organization of lipids in the human retina and optic nerve by MALDI imaging mass spectrometry.

Zemski Berry KA, Gordon WC, Murphy RC, Bazan NG.

Abstract: Matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI IMS) was used to characterize lipid species within sections of human eyes. Common phospholipids, such as PC(34:1), abundant in most tissues, were observed in accessory tissue, optic nerve, and retina. Triacylglycerols were highly localized in accessory tissue, whereas sulfatide and plasmalogen gylcerophosphoethanolamine (PE) lipids with a monounsaturated fatty acid were found enriched in optic nerves. Additionally, several lipids were associated solely with inner retina, photoreceptors, or retinal pigment epithelium; a plasmalogen PE lipid containing docosahexaenoic acid (DHA), PE(18:0p/22:6), was present exclusively in inner retina, and glycerophosphocholine (PC) and PE diacyl DHA-containing lipids were found solely in photoreceptors. PC lipids containing very long chain polyunsaturated fatty acids (VLC-PUFA) were detected in photoreceptors despite their low abundance in retina. Ceramide lipids and the bis-retinoid, A2E, were present only in retinal pigment epithelium. This MALDI IMS study readily revealed the location of many lipids that have been associated with degenerative retinal diseases. Complex lipid localization within retinal tissue provides a global view of lipid organization and initial evidence for specific functions in localized regions, offering opportunities to assess their significance in retinal diseases, such as macular degeneration, where lipids have been implicated in the disease process.

PMID: 24367044 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Dec 13;54(14):ORSF68-80. doi: 10.1167/iovs.13-12757.

Dry age-related macular degeneration: mechanisms, therapeutic targets, and imaging.

Bowes Rickman C, Farsiu S, Toth CA, Klingeborn M.

Abstract: Age-related macular degeneration is the leading cause of irreversible visual dysfunction in individuals over 65 in Western Society. Patients with AMD are classified as having early stage disease (early AMD), in which visual function is affected, or late AMD (generally characterized as either "wet" neovascular AMD, "dry" atrophic AMD or both), in which central vision is severely compromised or lost. Until recently, there have been no therapies available to treat the disorder(s). Now, the most common wet form of late-stage AMD, choroidal neovascularization, generally responds to treatment with anti-vascular endothelial growth factor therapies. Nevertheless, there are no current therapies to restore lost vision in eyes with advanced atrophic AMD. Oral supplementation with the Age-Related Eye Disease Study (AREDS) or AREDS2 formulation (antioxidant vitamins C and E, lutein, zeaxanthin, and zinc) has been shown to reduce the risk of progression to advanced AMD, although the impact was in neovascular rather than atrophic AMD. Recent findings, however, have demonstrated several features of early AMD that are likely to be druggable targets for treatment. Studies have established that much of the genetic risk for AMD is associated with complement genes. Consequently, several complement-based therapeutic treatment approaches are being pursued. Potential treatment strategies against AMD deposit formation and protein and/or lipid deposition will be discussed, including anti-amyloid therapies. In addition, the role of autophagy in AMD and prevention of oxidative stress through modulation of the antioxidant system will be explored. Finally, the success of these new therapies in clinical trials and beyond relies on early detection, disease typing, and predicting disease progression, areas that are currently being rapidly transformed by improving imaging modalities and functional assays.

PMID: 24335072 [PubMed - in process] PMCID: PMC3864379

Cell Mol Immunol. 2013 Dec 16. doi: 10.1038/cmi.2013.60. [Epub ahead of print]

The immunogenicity of cells derived from induced pluripotent stem cells.

Fu X.

Abstract: With their ability to undergo unlimited self-renewal in culture and to differentiate into all cell types in the body, human embryonic stem cells (hESCs) hold great potential for the treatment of currently incurable diseases. Two hESC-based cell therapies for spinal cord injury and macular degeneration have been advanced into human clinical trials. Despite this rapid progress, one key challenge of hESC-based cell therapy is the allogeneic immune rejection of hESC-derived cells by recipients. This problem could be mitigated by a recent breakthrough in the technology of induced pluripotent stem cells (iPSCs) by nuclear reprogramming of patient-specific somatic cells with defined factors, which could become a renewable source of autologous cells for cell therapy. However, recent studies revealing the abnormal epigenetics, genomic stability and immunogenicity of iPSCs have raised safety concerns over iPSC-based therapy. Recent findings related to the immunogenicity of iPSC derivatives will be summarized in this review.Cellular & Molecular Immunology advance online publication, 16 December 2013; doi:10.1038/cmi.2013.60.

PMID: 24336164 [PubMed - as supplied by publisher]

Ophthalmologica. 2013 Dec 12. [Epub ahead of print]

Age-Related Macular Degeneration Screening Using a Nonmydriatic Digital Color Fundus Camera and Telemedicine.

De Bats F, Vannier Nitenberg C, Fantino B, Denis P, Kodjikian L.

Purpose: To investigate the use of a nonmydriatic digital color fundus camera and telemedicine as screening tools for age-related macular degeneration (AMD).

Methods: Nonmydriatic color fundus photography was performed on patients consulting health examination centers and transmitted by telemedicine to an ophthalmology department. Rates for different grades of AMD were calculated and also statistically related to the presence or absence of risk factors.

Results: Among the 1,022 patients screened, a total of 1,363 color fundus photographs were interpreted, with 80% gradable images, allowing a diagnosis of AMD in 178 photographs. Among all the gradable images, 83.7% had no AMD (grade 0). The rates of AMD at grades 1, 2, 3 and 4 were 8%, 5.6%, 2.3% and 0.4%, respectively. A statistical odds ratio was found between the presence of AMD on fundus photographs and age, familial history of AMD or prior cataract surgery.

Conclusions: Nonmydriatic color fundus photography and telemedicine succeeded in screening for AMD.

PMID: 24356326 [PubMed - as supplied by publisher]

Ann Indian Acad Neurol. 2013 Oct;16(4):631-3. doi: 10.4103/0972-2327.120497.

Subacute sclerosing panencephalitis: A clinical appraisal.

Jagtap SA, Nair MD, Kambale HJ.

INTRODUCTION: Subacute sclerosing panencephalitis (SSPE) is a rare chronic, progressive encephalitis affecting primarily children and young adults, caused by a persistent infection of immune resistant measles virus. The aim of the present study is to describe the clinical profile and natural history of patients with SSPE.

METHODS: We collected data of patients with SSPE during 2004-2010 who fulfilled Dyken's criteria. We analyzed demographical, clinical, electrophysiological, and imaging features.

RESULTS: Study included 34 patients, 26 (76.5%) males with age of onset from 3 to 31 years. Twenty one patients were below 15 years of age formed childhood SSPE and 13 above 15 years of age constituted adult onset group. 85.3% had low-socioeconomic status. Eleven received measles vaccination and seven were unvaccinated. 59.9% patients had measles history. Most common presenting symptom was scholastic backwardness (52.5%) followed by seizures (23.5%). Three patients each had cortical blindness, macular degeneration, decreased visual acuity, and optic atrophy. Electroencephalographic (EEG) showed long interval periodic complexes and cerebrospinal fluid anti-measles antibody was positive in all. Magnetic resonance imaging was done in 70.5% with was abnormal in 52.5%. Mean incubation period of SSPE after measles was 9.6 years. The follow-up duration was 1-10 years, (average of 2 years). Only one patient died from available data of follow-up, 9 were stable and 10 deteriorated in the form of progression of staging.

CONCLUSION: SSPE is common in low-socioeconomic status. The profile of adult onset did not differ from childhood onset SSPE, except for a longer interval between measles infection and presence of the ophthalmic symptom as presenting feature in adult onset group.

PMID: 24339595 [PubMed] PMCID: PMC3841616

Eur J Ophthalmol. 2013 Dec 12:0. doi: 10.5301/ejo.5000412. [Epub ahead of print]

Photoreceptor layer changes overlying drusen in eyes with age-related macular degeneration associated with vitreomacular traction.

Theodossiadis PG, Theodoropoulou S, Stamatiou P, Datseris I, Theodossiadis GP.

Purpose:To investigate by spectral-domain optical coherence tomography (SD-OCT) changes of photoreceptor layers over drusen in cases of dry type age-related macular degeneration associated with vitreomacular traction (VMT).

Methods: Clinical examination, fluorescein angiography, fundus photography, and SD-OCT data were retrospectively studied for a consecutive series of 27 patients with drusen, pseudodrusen, and VMT. Control groups of 32 patients with VMT without drusen and 34 patients with drusen and pseudodrusen without VMT were also studied.

Results:The examination revealed disruption of the line corresponding to the inner segment ellipsoid (ISel), previously called inner segment/outer segment junction, of photoreceptor layer, and development of cystoid edema in significantly higher incidence in VMT associated with drusen group. 22 out of 32 eyes with VMT and drusen (68.75%) had disrupted ISel, compared to 8 out of 37 (21.6%) control eyes with drusen only and to 12 out of 37 (32.4%) control eyes with VMT only. Chi-square analysis showed significant association between drusen and pseudodrusen on fovea, VMT, and localization of ISel disruption. The changes of the ISel were mainly found in the area that corresponded to VMT. The SD-OCT revealed drusen throughout the macula and discontinuation of ISel only in the fovea in 4 of 32 (12.5%) eyes with VMT, whereas none of 37 control eyes with drusen only had similar appearance.

Conclusions: The drusen in association with the cystoid macular edema induced by vitreous traction contribute to the photoreceptor layer defect overlying drusen in the fovea. In addition, the number of drusen and pseudodrusen was increased in the area of the vitreous traction compared to the peripheral retina.

PMID: 24338584 [PubMed - as supplied by publisher]

Genet Mol Res. 2013 Dec 2;12(4):6140-8. doi: 10.4238/2013.December.2.11.

Fundus autofluorescence in exudative age-related macular degeneration.

Peng Q, Dong Y, Zhao PQ.

Abstract: The aim of this study was to investigate the characteristics of fundus autofluorescence (FAF) in patients with wet (exudative) age-related macular degeneration (AMD). Color fundus photographs, fundus fluorescein angiograms, indocyanine green angiograms, and FAF images were obtained from 61 patients (72 eyes) with exudative AMD. The FAF results for different patterns of exudative AMD were compared to those revealed by other fundus images. Of the 72 eyes evaluated, which were classified into three patterns based on the results of fundus fluorescein angiography, 68 had abnormal FAF. Forty-six eyes (63.9%) had classic wet AMD with abnormal FAF. Among these, 10 exhibited a slightly decreased FAF with near-normal or background FAF signal at the center of the lesion area; 36 demonstrated not only decreased FAF at the center of the lesion but also an increased FAF signal toward the lesion edge. Sixteen eyes (22.2%) had occult wet AMD, of which 12 exhibited heterogeneous fluorescence at the lesion site; 4 yielded normal FAF images. Ten eyes (13.9%) had a mixed pattern of wet AMD with abnormal FAF. FAF imaging suggested that the areas of blood and exudates decreased; however, fluorescence angiography revealed that lesions with hyperfluorescence had background or slightly increased FAF. These results showed that various patterns of wet AMD exhibit different autofluorescence characteristics. These represent the functional and metabolic features of retinal pigment epithelial cells. Therefore, FAF can be used to monitor disease development and evaluate the severity and prognosis of AMD.

PMID: 24338407 [PubMed - in process]

Pathogenesis

Invest Ophthalmol Vis Sci. 2013 Dec 12. pii: iovs.13-12978v1. doi: 10.1167/iovs.13-12978. [Epub ahead of print]

Systemic Upregulation of PDGF-B in Patients with Neovascular AMD.

Zehetner C, Kirchmair R, Neururer S, Kralinger MT, Bechrakis NE, Kieselbach GF.

Purpose: To determine the plasma levels of PDGF-B, VEGF and TNF-α in patients with neovascular age-related macular degeneration (AMD) and in patients with diabetic macular edema (DME).

Methods: 30 patients with neovascular AMD, 30 patients with DME and 12 healthy controls were included in this prospective study. The concentrations of PDGF-B, VEGF and TNF-α were measured by ELISA.

Results: The PDGF-B concentration in the plasma of controls was [median (25-75 percentile)] 263.5 (162.0 - 513.3) pg/ml and in patients with DME 219.0 (122.8 - 604.8) pg/ml. In patients with neovascular AMD PDGF-B levels were significantly higher with a median plasma concentration of 783.5 (289.3 - 1183.5) pg/ml (p=0.003). The VEGF concentrations in patients with DME 33.0 (21.8 - 73.0) pg/ml and in patients with neovascular AMD 55.0 (37.0 - 116.3) pg/ml showed no significant differences (p=0.159). A positive correlation of PDGF-B and VEGF plasma levels was found in patients with neovascular AMD and in patients with DME (r=0.683, p<0.001, and r=0.612, p<0.001 respectively). No significant differences of systemic TNF-α levels could be found between the three study groups.

Conclusions: Patients with neovascular AMD have significantly higher plasma PDGF-B levels compared to patients with DME and healthy controls. Our study data indicate that PDGF-B is involved in the disease process of neovascular AMD.

PMID: 24334449 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Dec 12. pii: iovs.13-11821v1. doi: 10.1167/iovs.13-11821. [Epub ahead of print]

Fcγ receptor upregulation is associated with immune-complex inflammation in the mouse retina and early age-related macular degeneration.

Murinello S, Mullins RF, J Lotery A, Perry VH, Teeling JL.

Purpose: Several lines of evidence suggest the involvement of antibodies and immune-complex inflammation in age-related macular degeneration (AMD), a blinding disease with a strong inflammatory component. To examine this further, we developed a novel experimental mouse model of retinal inflammation and evaluated whether inflammation associated with immune-complex formation was present in eyes of AMD donors.

Methods: A localised immune-complex mediated reaction was induced in the retina of wild-type (WT), Fcγ receptor γ chain deficient (γ-/-) and C1q deficient (C1q-/-) mice, and donor eyes were obtained post-mortem from donors with early or wet AMD and from healthy controls. The presence of immune-complexes, Fcγ receptors (FcγRs) and markers of macrophage/microglia activation was investigated by immunohistochemistry.

Results: In WT and C1q-/- mice, immune-complex deposition in the retina led to a robust inflammatory response with activation of microglia, recruitment of myeloid cells and increased expression of FcγRs I-IV and major histocompatibility complex class II (MHC II). This response was not observed in γ-/- mice, lacking activating FcγRs. We found that early AMD was associated with deposition of immunoglobulin G (IgG), C1q and membrane-attack-complex (MAC) in the choroiocapillaris, and increased numbers of CD45+ cells expressing FcγRIIa and FcγRIIb. Further, FcγRIIa and FcγRIIb were observed in eyes of donors suffering

from wet AMD.

Conclusions: Our studies suggest that immune-complexes may contribute to AMD pathogenesis through interaction of IgG with FcγRs and might inform about possible side effects associated with therapeutic antibodies.

PMID: 24334446 [PubMed - as supplied by publisher]

Ophthalmic Genet. 2013 Dec 12. [Epub ahead of print]

Bestrophin 1 - Phenotypes and Functional Aspects in Bestrophinopathies.

Pasquay C, Wang LF, Lorenz B, Preising MN.

Abstract: This is to review the current state of knowledge on the functional and clinical aspects of bestrophin 1, a prominent member of a family of proteins involved in the control and properties of the light peak of the EOG. Initially human bestrophin 1 gene (BEST1) mutations were identified to underlie Best vitelliform macular dystrophy (VMD), a dominantly inherited, juvenile-onset form of macular degeneration. In the recent past the phenotypical spectrum of retinal disorders associated with BEST1 mutations has been extended and the term bestrophinopathies was coined. The physiological role of bestrophin 1 is still not completely understood but has been linked to the generation of a transepithelial chloride current by controlling voltage-dependent calcium channels (VDCC). Dysfunction of bestrophin 1 may result in abnormal ion and fluid transport by the retinal pigment epithelium (RPE) disturbing and even disrupting direct interactions between the RPE and the photoreceptors.

PMID: 24328569 [PubMed - as supplied by publisher]

J Diabetes Res. 2013;2013:245271. doi: 10.1155/2013/245271. Epub 2013 Nov 25.

Ethyl Pyruvate Inhibits Retinal Pathogenic Neovascularization by Downregulating HMGB1 Expression.

Lee YM, Kim J, Jo K, Shin SD, Kim CS, Sohn EJ, Kim SG, Kim JS.

Abstract: Retinal pathogenic angiogenesis in the eyes is a causative factor in retinopathy of prematurity, diabetic retinopathy, and age-related macular degeneration. This study was designed to examine the pathogenic role of the high-mobility group box-1 (HMGB1) protein and the inhibitory effect of ethyl pyruvate (EP), a well-known antioxidant substance, in retinal pathogenic angiogenesis in mice with oxygen-induced retinopathy (OIR), one of the animal models of proliferative ischemic retinopathy. The OIR mouse model was used for our in vivo studies. The mice were exposed to 75% oxygen from postnatal day 7 (P7) to P11, after which the mice were brought to room air and intraperitoneally injected with EP (50 mg/kg, or 100 mg/kg) for five days. At P17, the mice were perfused with fluorescein isothiocyanate-dextran, and flat-mounted retinas were used to measure nonperfused and neovascular tufts. In OIR mice, an intraperitoneal injection of EP reduced the nonperfused retinal area in the treatment group and significantly reduced the retinal neovascular tufts. In addition, EP inhibited the overexpression of HMGB1 in the retinas of OIR mice. These data suggest that EP could serve as an innovative pharmaceutical agent to prevent retinal neovascularization through inhibiting HMGB1 expression.

PMID: 24371837 [PubMed - in process] PMCID: PMC3858882

J Clin Invest. 2013 Dec 20. pii: 69404. doi: 10.1172/JCI69404. [Epub ahead of print]

Melanocyte-secreted fibromodulin promotes an angiogenic microenvironment.

Adini I, Ghosh K, Adini A, Chi ZL, Yoshimura T, Benny O, Connor KM, Rogers MS, Bazinet L, Birsner AE, Bielenberg DR, D'Amato RJ.

Abstract: Studies have established that pigmentation can provide strong, protective effects against certain human diseases. For example, angiogenesis-dependent diseases such as wet age-related macular degeneration and infantile hemangioma are more common in light-skinned individuals of mixed European descent than in African-Americans. Here we found that melanocytes from light-skinned humans and albino mice secrete high levels of fibromodulin (FMOD), which we determined to be a potent angiogenic factor. FMOD treatment stimulated angiogenesis in numerous in vivo systems, including laser-induced choroidal neovascularization, growth factor-induced corneal neovascularization, wound healing, and Matrigel plug assays. Additionally, FMOD enhanced vascular sprouting during normal retinal development. Deletion of Fmod in albino mice resulted in a marked reduction in the amount of neovascularization induced by retinal vein occlusion, corneal growth factor pellets, and Matrigel plugs. Our data implicate the melanocyte-secreted factor FMOD as a key regulator of angiogenesis and suggest an underlying mechanism for epidemiological differences between light-skinned individuals of mixed European descent and African-Americans. Furthermore, inhibition of FMOD in humans has potential as a therapeutic strategy for treating angiogenesis-dependent diseases.

PMID: 24355922 [PubMed - as supplied by publisher]

PLoS One. 2013 Dec 20;8(12):e80288. doi: 10.1371/journal.pone.0080288.

IL-10 Is Significantly Involved in HSP70-Regulation of Experimental Subretinal Fibrosis.

Yang Y1, Takeda A1, Yoshimura T1, Oshima Y1, Sonoda KH2, Ishibashi T1.

Abstract: Subretinal fibrosis is directly related to severe visual loss, especially if occurs in the macula, and is frequently observed in advanced age-related macular degeneration and other refractory eye disorders such as diabetic retinopathy and uveitis. In this study, we analyzed the immunosuppressive mechanism of subretinal fibrosis using the novel animal model recently demonstrated. Both TLR2 and TLR4 deficient mice showed significant enlargement of subretinal fibrotic area as compared with wild-type mice. A single intraocular administration of heat shock protein 70 (HSP70), which is an endogenous ligand for TLR2 and TLR4, inhibited subretinal fibrosis in wild-type mice but not in TLR2 and TLR4-deficient mice. Additionally, HSP70 induced IL-10 production in eyes from wild-type mice but was impaired in both TLR2- and TLR4-deficient mice, indicating that HSP70-TLR2/TLR4 axis plays an immunomodulatory role in subretinal fibrosis. Thus, these results suggest that HSP70-TLR2/TLR4 axis is a new therapeutic target for subretinal fibrosis due to prognostic CNV.

PMID: 24376495 [PubMed - in process] PMCID: PMC3869650

Front Physiol. 2013 Dec 16;4:366.

Lipid peroxidation: pathophysiological and pharmacological implications in the eye.

Njie-Mbye YF1, Kulkarni-Chitnis M1, Opere CA2, Barrett A2, Ohia SE1.

Abstract: Oxygen-derived free radicals such as hydroxyl and hydroperoxyl species have been shown to oxidize phospholipids and other membrane lipid components leading to lipid peroxidation. In the eye, lipid peroxidation has been reported to play an important role in degenerative ocular diseases (age-related macular degeneration, cataract, glaucoma, diabetic retinopathy). Indeed, ocular tissues are prone to damage from reactive oxygen species due to stress from constant exposure of the eye to sunlight, atmospheric oxygen and environmental chemicals. Furthermore, free radical catalyzed peroxidation of long chain polyunsaturated acids (LCPUFAs) such as arachidonic acid and docosahexaenoic acid leads to generation of LCPUFA metabolites including isoprostanes and neuroprostanes that may further exert

pharmacological/toxicological actions in ocular tissues. Evidence from literature supports the presence of endogenous defense mechanisms against reactive oxygen species in the eye, thereby presenting new avenues for the prevention and treatment of ocular degeneration. Hydrogen peroxide (H2O2) and synthetic peroxides can exert pharmacological and toxicological effects on tissues of the anterior uvea of several mammalian species. There is evidence suggesting that the retina, especially retinal ganglion cells can exhibit unique characteristics of antioxidant defense mechanisms. In the posterior segment of the eye, H2O2 and synthetic peroxides produce an inhibitory action on glutamate release (using [3H]-D-aspartate as a marker), in vitro and on the endogenous glutamate and glycine concentrations in vivo. In addition to peroxides, isoprostanes can elicit both excitatory and inhibitory effects on norepinephrine (NE) release from sympathetic nerves in isolated mammalian iris ciliary bodies. Whereas isoprostanes attenuate dopamine release from mammalian neural retina, in vitro, these novel arachidonic acid metabolites exhibit a biphasic regulatory effect on glutamate release from retina and can regulate amino acid neurotransmitter metabolism without inducing cell death in the retina. Furthermore, there appears to be an inhibitory role for neuroprostanes in the release of excitatory amino acid neurotransmitters in mammalian retina. The ability of peroxides and metabolites of LCPUFA to alter the integrity of neurotransmitter pools provides new potential target sites and pathways for the treatment of degenerative ocular diseases.

PMID: 24379787 [PubMed - as supplied by publisher] PMCID: PMC3863722

J Ophthalmic Vis Res. 2013 Jul;8(3):244-56.

The ubiquitin-proteasome system and microvascular complications of diabetes.

Yadranji Aghdam S, Sheibani N.

Abstract: The ubiquitin-proteasome system (UPS) is the mainstay of protein quality control which regulates cell cycle, differentiation and various signal transduction pathways in eukaryotic cells. The timely and selective degradation of surplus and/or aberrant proteins by the UPS is essential for normal cellular physiology. Any disturbance, delay or exaggeration in the process of selection, sequestration, labeling for degradation and degradation of target proteins by the UPS will compromise cellular and tissue homeostasis. High blood glucose or hyperglycemia caused by diabetes disrupts normal vascular function in several target organs including the retina and kidney resulting in the development of diabetic retinopathy (DR) and diabetic nephropathy (DN). We and others have shown that hyperglycemia and oxidative stress modulate UPS activity in the retina and kidney. The majority of studies have focused on the kidney and provided insights into the contribution of dysregulated UPS to microvascular damage in DN. The eye is a unique organ in which a semi-fluid medium, the vitreous humor, separates the neural retina and its anastomosed blood vessels from the semi-solid lens tissue. The complexity of the cellular and molecular components of the eye may require a normal functioning and well tuned UPS for healthy vision. Altered UPS activity may contribute to the development of retinal microvascular complications of diabetes. A better understanding of the molecular nature of the ocular UPS function under normal and diabetic conditions is essential for development of novel strategies targeting its activity. This review will discuss the association of retinal vascular cell UPS activity with microvascular damage in DR with emphasis on alterations of the PA28 subunits of the UPS.

PMID: 24349668 [PubMed] PMCID: PMC3853777

Cell Death Dis. 2013 Dec 12;4:e965. doi: 10.1038/cddis.2013.478.

Induction of necrotic cell death by oxidative stress in retinal pigment epithelial cells.

Hanus J1, Zhang H2, Wang Z3, Liu Q4, Zhou Q1, Wang S5.

Abstract: Age-related macular degeneration (AMD) is a degenerative disease of the retina and the leading

cause of blindness in the elderly. Retinal pigment epithelial (RPE) cell death and the resultant photoreceptor apoptosis are characteristic of late-stage dry AMD, especially geographic atrophy (GA). Although oxidative stress and inflammation have been associated with GA, the nature and underlying mechanism for RPE cell death remains controversial, which hinders the development of targeted therapy for dry AMD. The purpose of this study is to systematically dissect the mechanism of RPE cell death induced by oxidative stress. Our results show that characteristic features of apoptosis, including DNA fragmentation, caspase 3 activation, chromatin condensation and apoptotic body formation, were not observed during RPE cell death induced by either hydrogen peroxide or tert-Butyl hydroperoxide. Instead, this kind of cell death can be prevented by RIP kinase inhibitors necrostatins but not caspase inhibitor z-VAD, suggesting necrotic feature of RPE cell death. Moreover, ATP depletion, receptor interacting protein kinase 3 (RIPK3) aggregation, nuclear and plasma membrane leakage and breakdown, which are the cardinal features of necrosis, were observed in RPE cells upon oxidative stress. Silencing of RIPK3, a key protein in necrosis, largely prevented oxidative stress-induced RPE death. The necrotic nature of RPE death is consistent with the release of nuclear protein high mobility group protein B1 into the cytoplasm and cell medium, which induces the expression of inflammatory gene TNFα in healthy RPE and THP-1 cells. Interestingly, features of pyroptosis or autophagy were not observed in oxidative stress-treated RPE cells. Our results unequivocally show that necrosis, but not apoptosis, is a major type of cell death in RPE cells in response to oxidative stress. This suggests that preventing oxidative stress-induced necrotic RPE death may be a viable approach for late-stage dry AMD.

PMID: 24336085 [PubMed - in process]

Cell Rep. 2013 Dec 26;5(6):1527-35. doi: 10.1016/j.celrep.2013.11.042.

Hypomethylation of the IL17RC Promoter in Peripheral Blood Leukocytes Is Not A Hallmark of Age-Related Macular Degeneration.

Oliver VF1, Franchina M2, Jaffe AE3, Branham KE4, Othman M4, Heckenlively JR4, Swaroop A5, Campochiaro B1, Vote BJ6, Craig JE7, Saffery R8, Mackey DA2, Qian J1, Zack DJ9, Hewitt AW10, Merbs SL11.

Abstract: Age-related macular degeneration (AMD) is a leading cause of visual impairment worldwide. Aberrant DNA methylation within the promoter of IL17RC in peripheral blood mononuclear cells has recently been reported in AMD. To validate this association, we examined DNA methylation of the IL17RC promoter in peripheral blood. First, we used Illumina Human Methylation450 Bead Arrays, a widely accepted platform for measuring global DNA methylation. Second, methylation status at multiple sites within the IL17RC promoter was determined by bisulfite pyrosequencing in two cohorts. Third, a methylation-sensitive quantitative PCR-based assay was performed on a subset of samples. In contrast to previous findings, we did not find evidence of differential methylation between AMD cases and age-matched controls. We conclude that hypomethylation within the IL17RC gene promoter in peripheral blood is not suitable for use as a clinical biomarker of AMD. This study highlights the need for considerable replication of epigenetic association studies prior to clinical application.

PMID: 24373284 [PubMed - in process]

Mutat Res. 2013 Dec 26. pii: S0027-5107(13)00198-X. doi: 10.1016/j.mrfmmm.2013.12.001. [Epub ahead of print]

Mutagenesis of mitochondrial DNA in Fuchs endothelial corneal dystrophy.

Czarny P1, Seda A1, Wielgorski M2, Binczyk E2, Markiewicz B1, Kasprzak E1, Jiménez-García MP3, Grabska-Liberek I4, Pawlowska E5, Blasiak J1, Szaflik J3, Szaflik JP6.

Abstract: Fuchs endothelial corneal dystrophy (FECD) is an age-related, slowly progressive disease, which may lead to loss of vision resulting from apoptosis of corneal endothelial (CE) cells, dysfunction of Descemet membrane (DM) and corneal edema. A growing body of evidence suggests that oxidative stress may play a major role in the pathogenesis of FECD and that mitochondria of CE cells are its main target. Mitochondrial DNA (mtDNA) is particularly prone to oxidative stress and changes in mtDNA were reported in FECD patients. In the present work we studied mtDNA damage and repair, mtDNA copy number, and the 4977 common deletion in mtDNA in DM cells and peripheral blood lymphocytes (PBLs) isolated from FECD patients. PBLs from 35 FECD patients and 32 controls were challenged for 10min with hydrogen peroxide at 20μ and then left in a fresh medium for 3h, resulting in a decrease in mtDNA copy number in both groups. Damage to mtDNA was not fully repaired after 3h and the extent of remaining lesions was significantly higher in the patients than the controls. We observed a higher copy number and an increased extent of mtDNA damage as well as a higher ratio of the common 4977bp deletion in DM cells of FECD patients than controls. Our results confirm that mutagenesis of mtDNA may be involved in FECD pathogenesis and disturbance in mtDNA sensitivity to damaging agent as well as changes in mtDNA damage repair along with alternations in mtDNA copy number may underline this involvement.

PMID: 24374226 [PubMed - as supplied by publisher]

Epidemiology

Invest Ophthalmol Vis Sci. 2013 Dec 13;54(14):ORSF5-ORSF13. doi: 10.1167/iovs.13-12789.

The prevalence of age-related eye diseases and visual impairment in aging: current estimates.

Klein R, Klein BE.

PURPOSE: To examine prevalence of five age-related eye conditions (age-related cataract, AMD, open-angle glaucoma, diabetic retinopathy [DR], and visual impairment) in the United States.

METHODS: Review of published scientific articles and unpublished research findings.

RESULTS: Cataract, AMD, open-angle glaucoma, DR, and visual impairment prevalences are high in four different studies of these conditions, especially in people over 75 years of age. There are disparities among racial/ethnic groups with higher age-specific prevalence of DR, open-angle glaucoma, and visual impairment in Hispanics and blacks compared with whites, higher prevalence of age-related cataract in whites compared with blacks, and higher prevalence of late AMD in whites compared with Hispanics and blacks. The estimates are based on old data and do not reflect recent changes in the distribution of age and race/ethnicity in the United States population. There are no epidemiologic estimates of prevalence for many visually-impairing conditions.

CONCLUSIONS: Ongoing prevalence surveys designed to provide reliable estimates of visual impairment, AMD, age-related cataract, open-angle glaucoma, and DR are needed. It is important to collect objective data on these and other conditions that affect vision and quality of life in order to plan for health care needs and identify areas for further research.

PMID: 24335069 [PubMed - in process]

Ophthalmology. 2013 Dec 11. pii: S0161-6420(13)01050-6. doi: 10.1016/j.ophtha.2013.10.043. [Epub ahead of print]

Incidence and Progression of Reticular Drusen in Age-Related Macular Degeneration: Findings from an Older Australian Cohort.

Joachim N1, Mitchell P1, Rochtchina E1, Tan AG1, Wang JJ2.

PURPOSE: To assess the 15-year incidence and progression of reticular drusen and associations of this lesion with age-related macular degeneration (AMD) risk factors.

DESIGN: Population-based cohort.

PARTICIPANTS: Blue Mountains Eye Study participants (n = 3654) 49 years of age and older attended baseline examinations; of these, 75.8%, 76.7%, and 56.1% of survivors attended 5-year, 10-year, and 15-year follow-up examinations, respectively.

METHODS: Color retinal photographs were obtained and comprehensive questionnaires were administered at each visit, and DNA samples were genotyped. Fundus autofluorescence images were not available. Reticular drusen identified from photographs were confirmed with side-by-side grading using the Wisconsin AMD grading protocol. Incidence was assessed using Kaplan-Meier product limit survival methods, controlling for competing risk of death. Associations between smoking, fish consumption, serum lipids, systemic and dietary factors, the CFH single nucleotide polymorphism (SNP) rs1061170 and ARMS2 SNP rs10490924, and the 15-year incidence of reticular drusen were analyzed in discrete logistic regression models. Generalized estimating equation models were used to analyze eye-specific relationships between these risk factors and 5-year progression from reticular drusen to late AMD.

MAIN OUTCOME MEASURES: Incidence and progression of reticular drusen.

RESULTS: The 15-year cumulative incidence of reticular drusen was 4.0% (n = 95). Increasing age (per decade increase; odds ratio [OR], 3.4; 95% confidence interval [CI], 2.6-4.4), female sex (OR, 2.0; 95% CI, 1.3-3.2), and presence of risk alleles of CFH-rs1061170 (OR, 1.8; 95% CI, 1.3-2.4) or ARMS2-rs10490924 (OR, 3.0; 95% CI, 2.1-4.4) were associated with higher reticular drusen incidence. Current smoking at baseline predicted higher reticular drusen incidence (OR 2.1, 95% CI 1.0-4.5) after adjusting for age, sex, CFH-rs1061170 and ARMS2-rs10490924 polymorphisms. Of 118 eyes with reticular drusen, 40 (33.9%) developed late AMD over 5 years. A higher proportion of eyes with reticular drusen located outside versus within the macular area progressed to late AMD (50.0% vs. 37.8%). Dietary lutein-zeaxanthin intake was associated with decreased likelihood of progression from reticular drusen to late AMD (adjusted OR, 0.5; 95% CI, 0.3-1.0).

CONCLUSIONS: Known AMD risk factors were associated with greater long-term risk of reticular drusen. Neither total area nor central location of reticular drusen predicted 5-year progression to late AMD. Increased consumption of lutein-zeaxanthin predicted a lower risk of progression.

PMID: 24332537 [PubMed - as supplied by publisher]

Zhonghua Yan Ke Za Zhi. 2013 Sep;49(9):795-800.

[Prevalence and causes of blindness and moderate and severe visual impairment among adults aged 50 years or above in Changji City of Xinjiang Uygur Autonomous Region:the China Nine-Province Survey].[Article in Chinese]

Ma XZ1, Zhao JL2, Ellwein LB, Wei B, Chen J, Ye Y, Tang XD, Yang M, Wang Y, Gao XC.

OBJECTIVE: To investigate the prevalence and causes of blindness and moderate and severe visual impairment among adults aged ≥ 50 years in Changji City of Xinjiang Uygur Autonomous Region, China.

METHODS: It was a population-based cross-section study.Geographically defined cluster sampling was used in randomly selecting 5714 individuals aged ≥ 50 years in Changji City. The survey was preceded by a pilot study where operational methods were refined and quality assurance evaluation was carried out. All participants were enumerated through village registers followed door-to-door visits.Eligible individuals were invited to received visual acuity measurement and eye examination. Prevalence of blindness and moderate and severe visual impairment was calculated according to different age, gender or education. And the reasons of blindness were analyzed.Statistical analyses were performed using Stata/SE Statistical

Software, release 9.0. Chi-square test was used to investigate the association of age, gender and education with presenting and best corrected visual acuity.

RESULTS: Five thousands seven hundreds and fourteen individuals were enumerated and 5250 persons were examined, the response rate was 91.88%. Based on the criteria of World Health Organization visual impairment classification in 1973, the prevalence of blindness and moderate and severe visual impairment defined as best corrected visual acuity was 0.74% (39/5250) and 3.83% (201/5250) respectively. The prevalence of blindness and moderate and severe visual impairment defined as presenting visual acuity was 1.33% (70/5250) and 8.02% (421/5250) respectively. The prevalence of blindness and moderate and severe visual impairment was higher in aged (trend $\chi(2) = 617.06$, $P = 0.000$) , illiterate (trend $\chi(2) = 222.35$, $P = 0.000$) persons. Cataract and was the first leading cause of blindness and visual impairment, the retinal diseases, including age-related macular degeneration, high myopic retinopathy, and diabetic retinopathy, were the second cause of blindness and visual impairment.Un-corrected refractive error was also the important cause of the visual blindness.

CONCLUSIONS: The prevalence of blindness and moderate and severe visual impairment is not high among older adults aged ≥ 50 years in Changji City. The first main causes of blindness and visual impairment includes cataract, retinal diseases and un-corrected refractive error.

PMID: 24330928 [PubMed - in process]

Am J Alzheimers Dis Other Demen. 2013 Dec 26. [Epub ahead of print]

Cognitive Dysfunction and Age-Related Macular Degeneration.

Rozzini L, Riva M, Ghilardi N, Facchinetti P, Forbice E, Semeraro F, Padovani A.

Abstract: Several previous studies showed that age-related macular degeneration (AMD) and Alzheimer's disease (AD) share common risk factors and histopathology changes, and there is epidemiological evidence linking AMD to cognitive impairment. We tested this theory in 51 patients with late-stage AMD and 24 controls by analyzing their neuropsychological profiles. In this study, data showed that patients affected by late-stage AMD have a worse global cognitive function than those of the controls and, in particular, show worse performances in memory tasks. Moreover, patients affected by the dry form of AMD are significantly impaired in executive functions in addition to memory. Data support the hypothesis of a possible association between AMD and cognitive impairment. In particular, patients affected by the dry form of AMD may be at greater risk of developing subsequent dementia.

PMID: 24370621 [PubMed - as supplied by publisher]

Ann Agric Environ Med. 2013 Dec 19;20(4):726-30.

Wet age-related macular degeneration (wet AMD) in rural and urban inhabitants in south-eastern Poland.

Latalska M1, Matysik-Woźniak A2, Bylina J3, Latalski M4, Rejdak R2, Mackiewicz J1, Jarosz MJ5.

Objective: Evaluation of the demographic profile of patients from south-eastern Poland treated due to wet age-related macular degeneration.

Material and methods: Data concerning 201 patients were analyzed (133 F/ 68 M), aged from 50 -91, (mean age 76 ± 8.6), with the wet form of age-related macular degeneration treated by intravitreal injections of vascular endothelial growth factor inhibiting drugs. The significance of the relationships between variables was investigated by means of chi-square test for independence. The differences between the empirical and theoretical sample distribution was examined by means of chi-square goodness-of-fit test.

The significance level was set at p=0.05.

Results: Analysis did not show any significant differences in the access to treatment with intravitreal injections of vascular endothelial growth factor inhibitors between the rural and urban patients. Urban males and females living in the rural areas received treatment statistically more often (p=0.05). No significant differences were observed with respect to either the waiting time for a visit in a specialist outpatient department, nor the duration of waiting for treatment. Patients from the rural and urban areas presented a similar degree of visual impairment, evidencing the advancement of the pathological process.

Conclusions: Place of residence has no effect on obtaining treatment by patients. The lack of significant differences in treatment between the rural and urban inhabitants may indicate a sufficient level of ophthalmological care in the area of south-eastern Poland. An improvement in the awareness of hazards resulting from inadequate diet and life style could exert a positive effect on the state of health of rural and urban inhabitants. At the same time, knowledge of the disease and risk of blindness related with this disease would increase alertness among rural and urban inhabitants, and in consequence, accelerate an early diagnosis and implementation of an effective treatment.

PMID: 24364443 [PubMed - in process]

Graefes Arch Clin Exp Ophthalmol. 2013 Dec 21. [Epub ahead of print]

Risk factors for exudative age-related macular degeneration in a large French case-control study.

Zerbib J, Delcourt C, Puche N, Querques G, Cohen SY, Sahel J, Korobelnik JF, Le Goff M, Souied EH.

PURPOSE: The purpose of the CAP (Creteil AMD PHRC-funded) Study was to analyze risk factors of exudative age-related macular degeneration (AMD) in a large French case-control population.

PATIENTS AND METHODS: One thousand and twenty-four patients with exudative AMD and 275 controls were recruited. Information about lifestyle, medical history, and dietary intake were collected. Associations of risk factors were estimated using logistic regression.

RESULTS: After multivariate adjustment, CFH Y402H and ARMS2 A69S polymorphisms were associated with very high risk for exudative AMD (OR = 6.21 and OR = 11.7, respectively, p < 0.0001). Risk for exudative AMD was increased in current smokers (OR = 3.79, p = 0.0003) and former smokers having quitted since less than 20 years ago (OR = 2.30, p = 0.002), but not in former smokers having quitted since 20 years or more ago (OR = 0.81, p = 0.43). Heavy smokers (at least 25 pack-years) were particularly at risk (OR = 3.61, p < 0.0001). Use of cooking oils rich in omega 3 fatty acids was significantly associated with a reduced risk of exudative AMD (OR = 0.55, 95 % CI: 0.36-0.84, p = 0.006), as well as a high consumption of fruits (OR = 0.60, 95 % CI: 0.37-0.98, p = 0.04), but not the consumption of fish, vegetables or oils rich in omega 6. High waist circumference was associated with increased risk for exudative AMD (OR = 2.53, p < 0.0001), but not hypercholesterolemia, hypertension, or body mass index.

CONCLUSIONS: The CAP Study confirms major genetic risk factors for exudative AMD. It further documents the high risk in heavy smokers and the long persistence of risk after smoking cessation, and the associations with waist circumference and fruit consumption. Furthermore, we observed an inverse correlation between AMD and cooking oils harboring a beneficial omega-3 fatty acid profile.

PMID: 24362810 [PubMed - as supplied by publisher]

Ophthalmologe. 2013 Dec 18. [Epub ahead of print]

[Increase in examinations for cataracts, glaucoma, diabetic retinopathy and age-related macular degeneration : Comparative cross-sectional study between 2010 and 1997 in ophthalmological

practices.] [Article in German]

Bertram B, Gante C, Hilgers RD.

BACKGROUND: The importance of the four most commonly occurring vision-threatening diseases, age-related macular degeneration (AMD), glaucoma, diabetic retinopathy and cataract in ophthalmological practices has changed due to demographic developments, medical progress and transference of inpatient treatment to the outpatient area of private practice.

METHODS: In the fourth quarter year of 2010 a survey of 15,125 patients (approximately 10 %) from 96 private ophthalmology practices (mean 149 patients per ophthalmologist, range 45-376) was carried out. The results for the four most commonly occurring vision-threatening diseases were compared with the result from a previous survey carried out for the fourth quarter year of 1997.

RESULTS: Compared to 1997 there was an increase in the age-adjusted proportion of examinations in 2010 for cataracts by 29 %, for glaucoma by 21 %, for diabetic retinopathy by 39 % and for vitreoretinal diseases by 19 %. The number of AMD examinations in the age group over 70 years old showed a particularly high increase.

CONCLUSIONS: The number of patients examined for the four most commonly occurring vision-threatening diseases increased from 1997 to 2010 not only in absolute numbers but also in relation to age. In the future financial and personnel resources must be made available for the early and guidelines-conform detection, diagnostics and therapy by ophthalmologists.

PMID: 24343245 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Dec 13. pii: S0161-6420(13)00888-9. doi: 10.1016/j.ophtha.2013.09.043. [Epub ahead of print]

Association between Visual Field Defects and Quality of Life in the United States.

Qiu M1, Wang SY1, Singh K2, Lin SC3.

PURPOSE: To investigate the association between visual field defects and quality of life in the United States population.

DESIGN: Cross-sectional study.

PARTICIPANTS: A total of 5186 participants in the 2005 through 2008 National Health and Nutrition Examination Survey 40 years of age and older without a self-reported history of age-related macular degeneration or prior refractive surgery who had undergone frequency doubling technology perimetric testing.

METHODS: Frequency doubling technology perimetry was performed in both eyes. Results from the better eye were used to categorize subjects as normal or having mild, moderate, or severe visual field loss. Subjects completed surveys about their visual and physical functioning ability.

MAIN OUTCOME MEASURES: Disability pertaining to 6 vision-related activities, 2 visual function questions, and 5 physical functioning domains.

RESULTS: Eighty-one percent of subjects had normal visual fields and 10%, 7%, and 2% demonstrated mild, moderate, and severe visual field defects, respectively. Subjects with greater severity of visual field defects had greater difficulty with vision-related activities. Subjects with severe visual field defects demonstrated the greatest odds of difficulty with all 6 activities. The 2 activities impacted most adversely were daytime driving in familiar places (odds ratio [OR], 12.4; 95% confidence interval [CI], 6.1-25.1) and noticing objects off to the side when walking (OR, 7.7; 95% CI, 4.7-12.7). Subjects with severe visual field defects had greater odds of worrying about eyesight (OR, 3.4; 95% CI, 2.0-5.8) and being limited by vision

in the time spent on daily activities (OR, 5.1; 95% CI, 3.0-8.5). Subjects with severe visual field defects demonstrated the greatest odds of difficulty with 3 physical function domains, including activities of daily living (OR, 2.45; 95% CI, 1.37-4.38), instrumental activities of daily living (OR, 2.45; 95% CI, 1.37-4.38), as well as leisure and social activities (OR, 3.29; 95% CI, 1.87-5.77).

CONCLUSIONS: Greater severity of visual field abnormality was associated with significantly greater odds of disability with vision-related function and physical function. These findings support the necessity of routine screening to find those who may benefit from therapy to prevent progressive glaucomatous vision loss.

PMID: 24342021 [PubMed - as supplied by publisher]

Oxid Med Cell Longev. 2013;2013:365046. doi: 10.1155/2013/365046. Epub 2013 Nov 30.

Superoxide dismutase1 levels in north Indian population with age-related macular degeneration.

Anand A1, Sharma NK1, Gupta A2, Prabhakar S1, Sharma SK3, Singh R2.

Aim: The aim of the study was to estimate the levels of superoxide dismutase1 (SOD1) in patients of age-related macular degeneration (AMD) and examine the role of oxidative stress, smoking, hypertension, and other factors involved in the pathogenesis of AMD. Methods. 115 AMD patients and 61 healthy controls were recruited for this study. Serum SOD1 levels were determined by ELISA and were correlated to various risk factors. Logistic regression model of authenticity, by considering SOD1 as independent variable, has been developed along with ROC curve.

Results: The SOD1 levels were significantly higher in AMD patients as compared to those of the controls. The difference was not significant for wet and dry AMD. However, the difference was significant between wet AMD subtypes. Nonsignificance of the Hosmer-Lemeshow goodness of fit statistic (χ (2) = 10.516, df = 8, P = 0.231) indicates the appropriateness of logistic regression model to predict AMD.

Conclusion: Oxidative stress in AMD patients may mount compensatory response resulting in increased levels of SOD1 in AMD patients. To predict the risk of AMD on the basis of SOD1, a logistic regression model shows authenticity of 78%, and area under the ROC curve (0.827, P = .0001) with less standard error of 0.033 coupled with 95% confidence interval of 0.762-0.891 further validates the model.

PMID: 24363822 [PubMed - in process] PMCID: PMC3864086

Eye (Lond). 2013 Dec 20. doi: 10.1038/eye.2013.256. [Epub ahead of print]

Myopia, an underrated global challenge to vision: where the current data takes us on myopia control.

Holden B1, Sankaridurg P1, Smith E2, Aller T3, Jong M4, He M5.

Abstract: Myopia is the most frequent cause of distance impairment in the world and is creating an alarming global epidemic with deleterious ramifications for the quality of life and economic health of individuals and nations as a whole. In addition to being immediately disadvantageous, myopia increases the risk of serious disorders such as myopic macular degeneration, retinal detachment, glaucoma, and cataract and is a leading cause of visual impairment and blindness across many countries. The reduction in age of onset of myopia is of great concern since the earlier the onset, the more myopic the individual will become, with all the attendant increased risks of accompanying debilitating eye conditions. The economic burden is great; both in consequences of uncorrected refractive error and also in the provision of devices for correcting visual acuity. Earlier onset of myopia increases the lifetime economic burden related to loss of productivity and independence, leading to a reduced quality of life. Recent data suggest addressing accommodation

per se has little direct amelioration of myopia progression. Pharmacological interventions that effect changes in the sclera show promising efficacy, whereas optical interventions based on a myopic shift in the retinal image are proving to effect up to 55% reduction in the rate of progression of myopia. Early contact lens and spectacle interventions that reduce the rate of progression of myopia are able to significantly reduce the burden of myopia. These non-pharmacological interventions show profound promise in reducing the overall associated morbidity of myopia.

PMID: 24357836 [PubMed - as supplied by publisher]

Pak J Med Sci. 2013 Sep;29(5):1203-7.

Prevalence of blindness and causes of visual impairment among adults aged 50 years or above in southern. Jiangsu Province of China.

Yao Y1, Shao J2, Sun W3, Zhu J4, Hong Fu D5, Guan H6, Liu Q7.

Objective: The prevalence of blindness and low vision among adults aged ≥50 years in southern Jiangsu Province were surveyed and estimated.

Methods: Cluster sampling was employed from January to September 2010 to randomly select 6,722 individuals aged ≥50 years in 28 clusters from southern Jiangsu Province. The survey was preceded by a pilot study, which refined operational methods and conducted quality assurance evaluation. Eligible individuals were registered for visual acuity measurement and eye examination.

Results: A total of 6,155 individuals were recruited, and a response rate of 91.50% was obtained. The prevalence of bilateral blindness and low vision were found to be 0.76% and 1.37%, respectively. Subjects with monocular blindness and low vision were 3.27% and 3.48%, respectively. Among the individuals evaluated, 201 were detected to have monocular blindness and 47 with bilateral blindness. In addition, 55 of the 201 subjects with monocular blindness were found to suffer from low vision of the other eye. Among the 295 subjects with blind eyes, 116 (39.32%), 31 (10.51%), and 28 (9.49%) were caused by cataract, high myopia macular degeneration, and atrophic eyeballs, respectively. In the 437 subjects with low-vision eyes, 223 (51.03%), 41 (9.38%), and 41 (9.38%) had cataract, high myopia macular degeneration, and age -related macular degeneration, respectively.

Conclusions: Blindness and low vision are caused by descending cataract, age-related macular degeneration, high myopia macular degeneration, and atrophic eyeballs.

PMID: 24353720 [PubMed] PMCID: PMC3858935

Kidney Int. 2013 Dec 11. doi: 10.1038/ki.2013.491. [Epub ahead of print]

Kidney and eye diseases: common risk factors, etiological mechanisms, and pathways.

Wong CW1, Wong TY2, Cheng CY2, Sabanayagam C3.

Abstract: Chronic kidney disease is an emerging health problem worldwide. The eye shares striking structural, developmental, and genetic pathways with the kidney, suggesting that kidney disease and ocular disease may be closely linked. A growing number of studies have found associations of chronic kidney disease with age-related macular degeneration, diabetic retinopathy, glaucoma, and cataract. In addition, retinal microvascular parameters have been shown to be predictive of chronic kidney disease. Chronic kidney disease shares common vascular risk factors including diabetes, hypertension, smoking, and obesity, and pathogenetic mechanisms including inflammation, oxidative stress, endothelial dysfunction, and microvascular dysfunction, with ocular diseases supporting the 'Common Soil Hypothesis.' In this review, we present major epidemiological evidence for these associations and explore underlying

pathogenic mechanisms and common risk factors for kidney and ocular disease. Understanding the link between kidney and ocular disease can lead to the development of new treatment and screening strategies for both diseases.Kidney International advance online publication, 11 December 2013; doi:10.1038/ki.2013.491.

PMID: 24336029 [PubMed - as supplied by publisher]

BMJ Open. 2013 Dec 30;3(12):e004146. doi: 10.1136/bmjopen-2013-004146.

Prevalence of ocular fundus pathology with type 2 diabetes in a Chinese urban community as assessed by telescreening.

Liu L, Geng J, Wu J, Yuan Z, Lian J, Desheng H, Chen L.

OBJECTIVE: To describe the telescreening model and assess the prevalence of ocular fundus pathology in patients with type 2 diabetes within a Chinese urban community.

DESIGN: Community-based cross-sectional study.

SETTING: Healthcare centre of Fengyutan Community, Shenyang, China.

PARTICIPANTS: A total 528 patients (287 females) with type 2 diabetes mellitus (DM) were randomly recruited using health files from the healthcare centre of Fengyutan community between 8 October and 20 November 2012.

MAIN OUTCOME MEASURES: Signs of any diabetic retinopathy (DR), signs of glaucoma and signs of age -related macular degeneration (AMD).

RESULTS: The main ocular fundus pathologies were DR (75 patients, 14.20%), 65 (86.67%) cases of which were newly detected, AMD (57 patients, 10.79%) and glaucoma (63 patients, 11.93%). The risk factors for fundus pathology were long duration of diabetes (OR 2.31, 95% CI 1.87 to 2.56), and higher fasting plasma glucose (OR 3.64, 95% CI 1.81 to 5.21) and glycated haemoglobin (HbA1c) levels (OR 3.83, 95% CI 1.87 to 6.35).

CONCLUSIONS: There was a high prevalence of fundus pathology among patients with type 2 diabetes, and in most of the cases, this was newly detected. Community screening for fundus pathology among patients with a long duration of type 2 diabetes and high fasting plasma glucose and HbA1c levels using a telescreening model will provide an effective strategy for the prevention and treatment of fundus pathology.

PMID: 24381259 [PubMed]

Genetics

J Innate Immun. 2013 Dec 7. [Epub ahead of print]

The Role of Complement in Age-Related Macular Degeneration: Heparan Sulphate, a ZIP Code for Complement Factor H?

Langford-Smith A, Keenan TD, Clark SJ, Bishop PN, Day AJ.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in developed nations and has been associated with complement dysregulation in the central retina. The Y402H polymorphism in the complement regulatory protein factor H (CFH) can confer a >5-fold increased risk of developing AMD and is present in approximately 30% of people of European descent. CFH, in conjunction with other factors, regulates complement activation in host tissues, and the Y402H polymorphism has been found to alter the

protein's specificity for heparan sulphate (HS) - a complex polysaccharide found ubiquitously in mammals. HS, which is present on the cell surface and also in the extracellular matrix, exhibits huge structural diversity due to variations in the level/pattern of sulphation, where particular structures may act as 'ZIP codes' for different tissue/cellular locations. Recent work has demonstrated that CFH contains two HS-binding domains that each recognize specific HS ZIP codes, allowing differential recognition of Bruch's membrane (in the eye) or the glomerular basement membrane (in the kidney). Importantly, the Y402H polymorphism impairs the binding of CFH to the HS in Bruch's membrane, which could result in increased complement activation and chronic local inflammation (in 402H individuals) and thereby contribute to AMD pathology.

PMID: 24335201 [PubMed - as supplied by publisher]

Neurogenetics. 2013 Dec 28. [Epub ahead of print]

Founder effect and ancestral origin of the spinocerebellar ataxia type 7 (SCA7) mutation in Mexican families.

García-Velázquez LE, Canizales-Quinteros S, Romero-Hidalgo S, Ochoa-Morales A, Martínez-Ruano L, Márquez-Luna C, Acuña-Alonzo V, Villarreal-Molina MT, Alonso-Vilatela ME, Yescas-Gómez P.

Abstract: Spinocerebellar ataxia type 7 (SCA7) is an autosomal dominant disease characterized by progressive cerebellar ataxia and macular degeneration causing progressive blindness. It accounts for 1 to 11.6 % of spinocerebellar ataxias (SCAs) cases worldwide and for 7.4 % of SCA7 cases in Mexico. We identified a cluster of SCA7 families who resided in a circumscribed area of Veracruz and investigated whether the high incidence of the disease in this region was due to a founder effect. A total of 181 individuals from 20 families were studied. Four microsatellite markers and one SNP flanking the ATNX7 gene were genotyped and the ancestral origin and local ancestry analysis of the SCA7 mutation were evaluated. Ninety individuals from 19 families had the SCA7 mutation; all were found to share a common haplotype, suggesting that the mutation in these families originated from a common ancestor. Ancestral origin and local ancestry analysis of SCA7 showed that the chromosomal segment containing the mutation was of European origin. We here present evidence strongly suggesting that the high frequency of SCA7 in Veracruz is due to a founder effect and that the mutation is most likely of European origin with greatest resemblance to the Finnish population.

PMID: 24374739 [PubMed - as supplied by publisher]

Prog Retin Eye Res. 2013 Dec 26. pii: S1350-9462(13)00083-9. doi: 10.1016/j.preteyeres.2013.12.004. [Epub ahead of print]

Nature and Nurture- Genes and Environment- Predict Onset and Progression of Macular Degeneration.

Sobrin L1, Seddon JM2.

Abstract: Age-related macular degeneration (AMD) is the most common cause of irreversible visual loss in the developed world. Both environmental and genetic factors contribute to the development of disease. Among environmental factors, smoking, obesity and dietary factors including antioxidants and dietary fat intake most consistently affect initiation and progression of AMD. There are also several lines of evidence that link both cardiovascular and inflammatory biomarkers to AMD. The genetic etiology of AMD has been and continues to be an intense and fruitful area of investigation. Genome-wide association studies have revealed many common variants associated with AMD and sequencing is increasing our knowledge of how rare variants impact disease. Evidence for specific interactions between environmental, therapeutic and genetic factors is emerging and elucidating the mechanisms of this interplay remains a major challenge in

the field. The knowledge of non-genetic, modifiable risk factors along with information about heritability and genetic risk variants for this disease acquired over the past 25 years have greatly improved patient management and our ability to predict which patients will develop or progress to advanced forms of AMD.

PMID: 24374240 [PubMed - as supplied by publisher]

J Ophthalmol. 2013;2013:453934. doi: 10.1155/2013/453934. Epub 2013 Nov 14.

Systems Biology Profiling of AMD on the Basis of Gene Expression.

Abu-Asab MS, Salazar J, Tuo J, Chan CC.

Abstract: Genetic pathways underlying the initiation and progression of age-related macular degeneration (AMD) have not been yet sufficiently revealed, and the correlations of AMD's genotypes, phenotypes, and disease spectrum are still awaiting resolution. We are tackling both problems with systems biology phylogenetic parsimony analysis. Gene expression data (GSE29801: NCBI, Geo) of macular and extramacular specimens of the retinas and retinal pigment epithelium (RPE) choroid complexes representing dry AMD without geographic atrophy (GA), choroidal neovascularization (CNV), GA, as well as pre-AMD and subclinical pre-AMD were polarized against their respective normal specimens and then processed through the parsimony program MIX to produce phylogenetic cladograms. Gene lists from cladograms' nodes were processed in Genomatix GePS to reveal the affected signaling pathway networks. Cladograms exposed a highly heterogeneous transcriptomic profiles within all the conventional phenotypes. Moreover, clades and nodal synapomorphies did not support the classical AMD phenotypes as valid transcriptomal genotypes. Gene lists defined by cladogram nodes showed that the AMD-related deregulations occurring in the neural retina were different from those in RPE-choroidal tissue. Our analysis suggests a more complex transcriptional profile of the phenotypes than expected. Evaluation of the disease in much earlier stages is needed to elucidate the initial events of AMD.

PMID: 24349763 [PubMed] PMCID: PMC3851728

Invest Ophthalmol Vis Sci. 2013 Dec 26. pii: iovs.13-12413v1. doi: 10.1167/iovs.13-12413. [Epub ahead of print]

Cfh genotype interacts with dietary glycemic index to modulate age-related macular degeneration-like features in mice.

Rowan S, Weikel KA, Chang ML, Nagel BA, Thinschmidt J, Carey AN, Grant MB, Fliesler SJ, Smith D, Taylor A.

Purpose: Age-related macular degeneration (AMD) is a leading cause of visual impairment worldwide. Both genetics and diet contribute to the relative risk for developing AMD, but their interactions are poorly understood. Genetic variations in Complement Factor H (CFH), and dietary glycemic index (GI) are major risk factors for AMD. We explored the effects of GI on development of early AMD-like features and changes to CNS inflammation in Cfh-null mice.

Methods: 11-week old wildtype C57Bl/6J or Cfh-null mice were group pair-fed high or low GI diets for 33 weeks. At 10-months of age, mice were evaluated for early AMD-like features in the neural retina and retinal pigmented epithelium (RPE) by light and electron microscopy. Brains were analyzed for Iba1 macrophage/microglia immunostaining, an indicator of inflammation.

Results: 10-month old wildtype mice showed no retinal abnormalities on either diet. Cfh-null mice, however, showed distinct early AMD-like features in the RPE when fed a low GI diet, including vacuolation, disruption of basal infoldings, and increased basal laminar deposits. Cfh-null mice also showed thinning of the RPE, hypopigmentation, and increased numbers of Iba1-expressing macrophages in the brain, irrespective of

diet.

Conclusions: The presence of early AMD-like features by 10-months of age in Cfh-null mice fed a low GI diet is surprising, given the apparent protection from the development of such features in aged WT mice or humans consuming lower GI diets. Our findings highlight the need to consider gene-diet interactions when developing animal models and therapeutic approaches to treat AMD.

PMID: 24370827 [PubMed - as supplied by publisher]

Mediators Inflamm. 2013;2013:435607. Epub 2013 Nov 27.

Mechanism of Inflammation in Age-Related Macular Degeneration: An Up-to-Date on Genetic Landmarks.

Parmeggiani F1, Sorrentino FS1, Romano MR2, Costagliola C3, Semeraro F4, Incorvaia C1, D'Angelo S1, Perri P1, De Nadai K5, Bonomo Roversi E6, Franceschelli P6, Sebastiani A1, Rubini M6.

Abstract: Age-related macular degeneration (AMD) is the most common cause of irreversible visual impairment among people over 50 years of age, accounting for up to 50% of all cases of legal blindness in Western countries. Although the aging represents the main determinant of AMD, it must be considered a multifaceted disease caused by interactions among environmental risk factors and genetic backgrounds. Mounting evidence and/or arguments document the crucial role of inflammation and immune-mediated processes in the pathogenesis of AMD. Proinflammatory effects secondary to chronic inflammation (e.g., alternative complement activation) and heterogeneous types of oxidative stress (e.g., impaired cholesterol homeostasis) can result in degenerative damages at the level of crucial macular structures, that is photoreceptors, retinal pigment epithelium, and Bruch's membrane. In the most recent years, the association of AMD with genes, directly or indirectly, involved in immunoinflammatory pathways is increasingly becoming an essential core for AMD knowledge. Starting from the key basic-research notions detectable at the root of AMD pathogenesis, the present up-to-date paper reviews the best-known and/or the most attractive genetic findings linked to the mechanisms of inflammation of this complex disease.

PMID: 24369445 [PubMed - as supplied by publisher] PMCID: PMC3863457

Invest Ophthalmol Vis Sci. 2013 Dec 13;54(14):ORSF28-30. doi: 10.1167/iovs.13-13234.

Genetic and environmental underpinnings to age-related ocular diseases.

Seddon JM.

Abstract: Age-related macular degeneration (AMD), cataract, glaucoma and diabetic retinopathy are common causes of visual loss. Both environmental and genetic factors contribute to the development of these diseases. The modifiable factors related to some of these age-related and visually threatening diseases are smoking, obesity, and dietary factors, and a cardiovascular risk profile. Many common and a few rare genetic factors are associated with AMD. The role of genetic variants for the other diseases are less clear. Interactions between environmental, therapeutic, and genetic factors are being explored. Knowledge of genetic risk and environmental factors, especially for AMD, has grown markedly over the past 2.5 decades and has led to some sight-saving approaches in preventive management.

PMID: 24335064 [PubMed - in process] PMCID: PMC3864375

Ophthalmic Genet. 2013 Dec 30. [Epub ahead of print]

Association of LOC387715/ARMS2 (rs10490924) Gene Polymorphism with Age-related Macular

Degeneration in the Brazilian Population.

Hirata FE, Vasconcellos JP, Medina FM, Rim PH, Fulco EA, Melo MB.

Background: An association between LOC387715/ARMS2 (rs10490924) gene polymorphism and AMD has been reported. The aim of this study was to evaluate whether this polymorphism is associated with AMD in a Brazilian cohort.

Materials and Methods: In total, 126 unrelated AMD patients (mean age 74.17 ± 7.64) were compared with 86 healthy controls (mean age 71.82 ± 7.12). Study subjects were classified according to the International ARM Epidemiological Study Group definition for early and late-stage AMD. LOC387715/ARMS2 rs10490924 polymorphism was evaluated through polymerase chain reaction and direct sequencing.

Results: The T allele frequency was significantly higher in AMD patients than in controls (39.6% compared to 20.3%). The odds ratio (OR) for AMD was 2.05 (95% CI 1.13-3.71) for heterozygotes (TG) and 8.32 (95% CI 2.30-45.99) for homozygotes (TT).

Conclusions: These results suggest that there is a contribution of the rs10490924 SNP of the LOC387715/ ARMS2 gene to AMD susceptibility in this sample of the Brazilian population.

PMID: 24372405 [PubMed - as supplied by publisher]

Diet & lifestyle

Invest Ophthalmol Vis Sci. 2013 Dec 17. pii: iovs.13-13216v1. doi: 10.1167/iovs.13-13216. [Epub ahead of print]

Genetic Evidence for Role of Carotenoids in Age-Related Macular Degeneration in the Carotenoids in Age-Related Eye Disease Study (CAREDS).

Meyers KJ, Mares JA, Igo RP Jr, Truitt B, Liu Z, Millen AE, Klein ML, Johnson EJ, Engelman CD, Karki CK, Blodi BA, Gehrs KM, Tinker L, Wallace RB, Robinson J, Leblanc ES, Sarto GE, Bernstein PS, Sangiovanni JP, Iyengar SK.

Purpose: To test variants in genes related to carotenoid status for association with age-related macular degeneration (AMD) in the Carotenoids in Age-Related Eye Disease Study (CAREDS).

Methods: 1,663 of 2,005 CAREDS participants were graded for AMD from fundus photography and genotyped for 424 single nucleotide polymorphisms (SNPs) from 24 candidate genes for carotenoid status. There were 337 AMD cases, 91% of which had early or intermediate AMD. SNPs were individually tested for association with AMD using logistic regression. A carotenoid-related genetic risk model was built using backward selection and compared to existing AMD risk factors using the area under the receiver operating characteristic curve (AUC).

Results: 24 variants from nine genes related to carotenoid status were individually associated with AMD after adjusting for age and ancestry. These include variants in genes related to 1) cholesterol and carotenoid membrane transport proteins in the intestine and retina (SCARB1, NPCL1L1, ABCA1), 2) high density lipoprotein levels in blood (SCARB1, APOE and ABCA1), 3) carotenoid cleavage (BCMO1 and BCO2), 4) omega-3 fatty acid status (FADS2) and 5) an inherited retinopathy associated with the complete absence of macular pigment (ALDH3A2). Nine of these variants were included in a genetic risk score which significantly contributed to the AUC of a model including age, smoking, CFH Y402H and ARMS2 A69S (AUC=0.72 versus 0.69, P-value=0.002).

Conclusion: Variants in genes related to carotenoid status are associated with AMD in CAREDS, adding to the body of molecular and epidemiological evidence supporting a protective role of carotenoids in risk of AMD.

PMID: 24346170 [PubMed - as supplied by publisher]

Rev Med Chir Soc Med Nat Iasi. 2013 Apr-Jun;117(2):328-33.

University of medicine and pharmacy "Grigore T. Popa" - Lasi Faculty of Medicine.

Dănulescu R, Costin D.

AIM: To establish the role of oxidative stress in retinal structural lesions in AMD and to monitor the evolution of oxidative stress markers and OCT measurements before and after treatment.

MATERIAL AND METHODS: This is a case-control study that included 19 patients diagnosed with AMD and 40 matched healthy controls. According to the AREDS classification, patients were divided into mild, moderate and severe AMD and received treatment with antioxidants, neurotrophic drugs, intravitreal corticosteroids and/or anti-VEGF. We followed the patients by assessment of visual acuity, optical coherence tomography (OCT) and oxidative stress markers, such as superoxide-dismutase (SOD), thiobarbituric acid reactive substances (TBARS), and C-reactive protein (CRP) from blood samples before and after treatment.

RESULTS: The OCT showed that the macular edema in patients with severe disease was significantly reduced after treatment, while the cases with normal retinal thickness increased significantly ($p = 0.005$). Comparing the mean values of SOD, TBARS and CRP in the two groups, we found that they were significantly higher in the study group compared to controls ($p < 0.01$), being higher in patients with severe disease. These values decreased post treatment, but they were still higher than in controls.

CONCLUSIONS: The present research supports the role of oxidative stress and inflammation in AMD and highlights the role of therapy directed against these risk factors. By monitoring the oxidative stress markers in the evolution of the disease, we showed that high values persist after treatment, thus supporting the idea that treatment should be followed for a long time.

PMID: 24340512 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2013 Dec 13;54(14):ORSF42-7. doi: 10.1167/iovs13-12914.

Nutrition effects on ocular diseases in the aging eye.

Chew EY.

PURPOSE: We reviewed the data from the clinical trials of nutritional supplements for the treatment of age-related cataract and age-related macular degeneration (AMD) to determine future directions of research and treatment.

METHODS: Data from the controlled clinical trials are presented and reviewed for potential opportunities for further research into the treatment of cataracts and AMD.

RESULTS: Two trials using daily multivitamins/minerals demonstrated a reduction in the progression of nuclear cataract, but increased the risk of posterior subcapsular cataract. For AMD, the Age-Related Eye Disease Study (AREDS) formulation (vitamins C, E, beta-carotene, zinc, and copper) reduced the risk of progression to advanced AMD by 25% at 5 years. Because beta-carotene is associated with increased lung cancer in former smokers, lutein/zeaxanthin could replace beta-carotene and provide an incremental increase in the beneficial effects beyond the effects of the AREDS formulation. In addition, a randomized clinical trial of B vitamins demonstrated a beneficial effect for AMD with the vitamin B complex.

CONCLUSIONS: Future evaluation may include additional assessments of nutrients for the treatment of progression of cataract and AMD. A modest reduction would have significant impact as the numbers of persons affected with these two leading causes of blindness are projected to double in the next decade. An important step would be to develop surrogate outcomes to increase efficiency in clinical trials. More detailed phenotyping, especially of AMD, is required as it appears to be not one disease, but a group of diseases.

Genotype-phenotype analyses may help to target pathways that are important in AMD.

PMID: 24335067 [PubMed - in process]

J Ophthalmol. 2013;2013:895147. Epub 2013 Dec 4.

Smoking and Age-Related Macular Degeneration: Review and Update.

Velilla S1, García-Medina JJ2, García-Layana A3, Dolz-Marco R4, Pons-Vázquez S5, Pinazo-Durán MD6, Gómez-Ulla F7, Arévalo JF8, Díaz-Llopis M9, Gallego-Pinazo R10.

Abstract: Age-related macular degeneration (AMD) is one of the main socioeconomical health issues worldwide. AMD has a multifactorial etiology with a variety of risk factors. Smoking is the most important modifiable risk factor for AMD development and progression. The present review summarizes the epidemiological studies evaluating the association between smoking and AMD, the mechanisms through which smoking induces damage to the chorioretinal tissues, and the relevance of advising patients to quit smoking for their visual health.

PMID: 24368940 [PubMed - as supplied by publisher] PMCID: PMC3866712

Clin Ophthalmol. 2014;4:15-21. doi: 10.2147/OPTH.S55080. Epub 2013 Dec 9.

In patients with neovascular age-related macular degeneration, physical activity may influence C-reactive protein levels.

Subhi Y, Singh A, Falk MK, Sørensen TL.

PURPOSE: Association of neovascular age-related macular degeneration (AMD) with C-reactive protein (CRP) was previously reported, indicating a relation to systemic low-grade inflammation. However, visual impairment limits physical activity, and physical activity modulates CRP levels. Here, we investigated the impact of physical activity on CRP levels in patients with neovascular AMD and control individuals.

SUBJECTS AND METHODS: We recruited participants from our outpatient AMD program, and control individuals from non-AMD patients, visitors, and department staff. After initial screening of 191 individuals, we included 98 patients with neovascular AMD and 77 controls. All were screened using digital fundus photography and optical coherence tomography, and interviewed about medical history and physical activity. Venous blood samples were obtained for high-sensitivity CRP.

RESULTS: Physically active individuals had lower CRP than physically inactive individuals (P=0.003), and physical activity was associated with lower CRP in patients (P=0.038) and controls (P=0.031). Patients and controls did not differ in percentage physically active (P=0.807) or in overall CRP levels (P=0.394). The independent contribution of physical activity on CRP was confirmed in a multiple regression analysis (P=0.009), in which the presence of neovascular AMD did not contribute significantly (P=0.913).

CONCLUSION: Our findings suggest that elevated CRP levels in patients with neovascular AMD are at least partly explained by physical inactivity. Future studies of systemic inflammation among the visually impaired should include disease-related implications, such as the impact of physical activity.

PMID: 24363550 [PubMed] PMCID: PMC3862739

Clin Experiment Ophthalmol. 2013 Dec 24. doi: 10.1111/ceo.12290. [Epub ahead of print]

Review of the role of refined dietary sugars (fructose & glucose) in the genesis of retinal disease.

Kearney FM, Fagan XJ, Al-Qureshi S.

Abstract: Sugar (sucrose) is a disaccharide comprising fructose monosaccharide and glucose monosaccharide. Fructose by itself is also added to sweeten a wide array of processed foods. Sugar consumption in the typical Western diet has increased significantly in the last four decades. It is sweeter than glucose.1 It is consumed from cradle to grave, given to babies as an analgesic and pacifier during medical procedures2, and children as a reward for good behaviour. In particular the consumption of sugar containing beverages, such as soft drinks and fruit juices, now represents a high proportion of total daily caloric intake. Fructose and glucose are metabolised differently by the body, and it appears to be fructose, which has a greater potential for a detrimental health outcome. In comparison to an isocaloric intake of glucose over 10 weeks, fructose was shown to result in higher visceral adipose tissue, elevated triglycerides and insulin resistance.3 This biochemical malfunction is a key contributor to the development of the metabolic syndrome. This review will provide a history of sugar consumption, fructose metabolism in particular and the numerous downstream cellular and molecular effects of this process. Finally, this article will examine the evidence that links fructose metabolism with the specific pathogenesis of ocular diseases. An understanding of the important roles played by dietary sugars in general, and fructose in particular, in the aetiology of the metabolic syndrome and diabetic retinopathy is of great value in implementing strategies for health behaviour change at the individual patient and community levels.