

Issue 207

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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.

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Drug treatment

Retina. 2014 Nov 10. [Epub ahead of print]

GEOGRAPHIC ATROPHY IN PATIENTS RECEIVING ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Xu L, Mrejen S, Jung JJ, Gallego-Pinazo R, Thompson D, Marsiglia M, Freund KB.

PURPOSE: To examine factors associated with the apparent growth of geographic atrophy (GA) in a consecutive series of eyes with treatment-naïve neovascular age-related macular degeneration receiving intravitreal anti-vascular endothelial growth factor therapy on a treat-and-extend regimen.

METHODS: This was a retrospective cohort study. Two independent graders identified areas of GA using near-infrared reflectance imaging and spectral domain optical coherence tomography (SD-OCT). Neovascular lesion subtypes were classified based on fluorescein angiography (FA) as occult choroidal neovascularization, classic choroidal neovascularization, retinal angiomatous proliferation, or mixed choroidal neovascularization, and by the anatomical classification system which utilizes FA and SD-OCT as Types 1 (sub-retinal pigment epithelium), 2 (subretinal), 3 (intraretinal), or mixed neovascularization.

RESULTS: Ninety-one patients (94 eyes) fit the inclusion criteria, of which 52 eyes (55.3%) experienced apparent GA growth. The odds of developing apparent GA were significantly lower in Type 1 neovascularization compared to the other lesion types ($P < 0.001$). Using both FA and SD-OCT to classify neovascular age-related macular degeneration significantly improves the goodness of fit in the correlation between apparent GA growth and baseline neovascular lesion type ($P < 0.001$).

CONCLUSION: Treatment-naïve neovascular age-related macular degeneration eyes with Type 1 neovascularization at baseline were less likely to develop GA than eyes with other types. The correlation between apparent GA growth and subtype of neovascularization is stronger when lesions are classified with an anatomic grading that utilizes both FA and SD-OCT.

PMID: 25387047 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2014 Nov 13. [Epub ahead of print]

Effects of aflibercept for ranibizumab-resistant neovascular age-related macular degeneration and polypoidal choroidal vasculopathy.

Kawashima Y, Oishi A, Tsujikawa A, Yamashiro K, Miyake M, Ueda-Arakawa N, Yoshikawa M, Takahashi A, Yoshimura N.

PURPOSE: To evaluate visual and anatomic outcomes in response to the conversion of treatment in patients with neovascular age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) refractory to previous treatment. We also investigated the effect of genetic factors.

METHODS: We recruited patients with AMD or PCV refractory to ranibizumab and initiated aflibercept treatment. Changes in the logarithm of minimum angle of resolution (logMAR) and central retinal thickness (CRT) measured using optical coherence tomography (OCT) 6 months after the conversion were compared between the AMD and PCV groups. We also genotyped each patient for the ARMS2 A69S, CFH Y402H, and I62V alleles, and investigated the association between genotype and treatment response.

RESULTS: Mean age of the participants was 75.6 ± 8.0 years. There were 15 patients with AMD and 26 patients with PCV. While PCV patients gained about 1 line of vision (0.40 ± 0.37 to 0.31 ± 0.40 , $P = 0.003$), AMD patients did not show significant improvement (0.41 ± 0.37 to 0.42 ± 0.39 , $P = 0.699$) despite the decrease in CRT (202.1 ± 113.7 to 131.2 ± 55.7 μm , $P = 0.003$). The prevalence of dry retina after treatment was higher among PCV patients (80.8 vs 46.7 %, $P = 0.024$). There was no significant difference between patients with risk and non-risk alleles for ARMS2 A69S, CFH Y402H, and I62V.

CONCLUSION: In AMD or PCV patients refractory to ranibizumab, switching to aflibercept is generally effective regardless of patient genotype. PCV patients may benefit more significantly than AMD patients.

PMID: 25391986 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Nov 13. [Epub ahead of print]

Efficacy of Intravitreal Injection of Aflibercept in Neovascular Age-Related Macular Degeneration with or without Choroidal Vascular Hyperpermeability.

Hata M, Oishi A, Tsujikawa A, Yamashiro K, Miyake M, Ooto S, Tamura H, Nakanishi H, Takahashi A, Yoshikawa M, Yoshimura N.

PURPOSE: To compare therapeutic responses to intravitreal aflibercept and ranibizumab in neovascular age-related macular degeneration (AMD)-affected eyes with and without choroidal vascular hyperpermeability (CVH).

METHODS: Medical records of 216 consecutive patients (216 eyes) with treatment-naïve exudative AMD who had received 3 monthly intravitreal injections of aflibercept (2 mg) and ranibizumab (0.5 mg) at a single institution were analyzed. The associations of CVH with functional and morphologic changes were compared between the treatment groups.

RESULTS: Although foveal thickness ($P = 0.85$) and visual acuity ($P = 0.13$) changes were not significantly different between the treatment groups, subfoveal choroidal thickness (CT) ($P = 0.001$) and pigment epithelial detachment (PED) height ($P = 0.043$) decreased more profoundly in the aflibercept-treated group. The incidence of dry macula after treatments was lower in the ranibizumab-treated eyes with CVH than in those without CVH ($P = 0.043$), but it showed no significant difference between the aflibercept-treated eyes with and without CVH ($P = 0.74$). The aflibercept-treated eyes with CVH showed a higher incidence of dry macula ($P = 0.04$) and greater decrease in subfoveal CT ($P = 0.002$) than the ranibizumab-treated eyes with CVH.

CONCLUSIONS: Intravitreal aflibercept can achieve remission of exudative retinal changes in eyes with AMD even in the presence of CVH. In addition, it showed greater effects on the choroid and PED than intravitreal ranibizumab, which may contribute to additional therapeutic effect on eyes with CVH in the long term. The possible relationship between CVH suppression and decrease in CT warrants further study.

PMID: 25395483 [PubMed - as supplied by publisher]

Retin Cases Brief Rep. 2014 Jun 18. [Epub ahead of print]

EARLY DETECTION OF CHOROIDAL NEOVASCULARIZATION FACILITATED WITH A HOME MONITORING PROGRAM IN AGE-RELATED MACULAR DEGENERATION.

Chaikitmongkol V, Bressler NM, Bressler SB.

PURPOSE: To describe clinical and imaging findings in two eyes with new onset subtle neovascular age-related macular degeneration that was detected by the regular use of a home monitoring device based on preferential hyperacuity visual field testing.

METHODS: Interventional case report.

RESULTS: Case 1, an 82-year-old man with the intermediate stage of age-related macular degeneration in both eyes, had been using the ForeseeHome device for 2 years when a change in test scores prompted an examination (an alert visit) to search for choroidal neovascularization (CNV) in his right eye. He denied any vision changes, and visual acuity remained 20/20 in the right eye. Fundus examination showed large drusen without any signs of CNV. The late phase of a fluorescein angiogram showed a small juxtafoveal area of subretinal leakage which corresponded to an intraretinal cystoid abnormality on optical coherence tomography. Intravitreal ranibizumab therapy was initiated, and the patient has maintained excellent visual acuity for at least 1 year. Case 2, a 67-year-old woman, had been using the home device for 3 months when an alert notification was prompted in the left eye. On notification, she recognized that she had had a subtle change in her vision in that eye with new distortion. Visual acuity decreased to 20/32 in the left eye. Fundus examination revealed stable confluent drusen without any apparent fluid, blood, or lipid. No definite fluorescein angiogram leakage was identified among the hyperfluorescent staining of extensive drusen. However, optical coherence tomography showed a cystoid abnormality in the inner plexiform layer prompting the initiation of intravitreal ranibizumab under the assumption that the changes represented CNV.

CONCLUSION: The home monitoring device has been proven to facilitate early detection of CNV associated with age-related macular degeneration. These two cases highlight early diagnosis of CNV heralded by the device. Visual acuity remained 20/32 or better, minimal or no fluorescein angiogram leakage was found, and subtle cystoid abnormalities appeared on optical coherence tomography.

PMID: 25383857 [PubMed - as supplied by publisher]

Retin Cases Brief Rep. 2013 Fall;7(4):304-6.

Purtscher-like retinopathy associated with pemphigus vulgaris.

Mariani AF, Major JC Jr, Brown DM, Wykoff CC, Benz MS, Kegley EN.

PURPOSE: To report a case of Purtscher-like retinopathy associated with pemphigus vulgaris.

METHOD: Case report of a 25-year-old Hispanic male who was referred for sudden and severe reduction of vision from his right eye shortly after an exacerbation of pemphigus vulgaris.

RESULTS: Fundus examination of the right eye revealed severe macular edema, nerve fiber layer infarcts, flame-shaped hemorrhages, and venous dilation. Fluorescein angiography and optical coherence tomography findings of flecken, ischemia with subsequent nerve fiber layer atrophy, and capillary leakage were consistent with Purtscher-like retinopathy. The patient was treated with 5 consecutive monthly intravitreal injections of 0.5 mg of ranibizumab. Visual acuity improved with resolution of macular edema, and the patient was started on systemic mycophenolate mofetil. Continued ocular stability was achieved with 11 subsequent intravitreal injections over the following 2 years.

CONCLUSION: Purtscher-like retinopathy may have been associated with pemphigus vulgaris through a

complement activation process that is previously undescribed. Retinal findings were successfully mitigated with the use of intravitreal anti-vascular endothelial growth factor therapy.

PMID: 25383823 [PubMed - in process]

Retin Cases Brief Rep. 2013 Fall;7(4):355-8.

Sequential, acute noninfectious uveitis associated with separate intravitreal injections of bevacizumab and ranibizumab.

Cunningham MA, Tlucek P, Folk JC, Boldt HC, Russell SR.

PURPOSE: To report the unique response of a patient with exudative age-related macular degeneration who developed sequential episodes of acute noninfectious uveitis following separate intravitreal injections of bevacizumab and ranibizumab.

METHODS: Retrospective interventional case report. Chart review.

RESULTS: A 73-year-old white woman, who received monthly intravitreal bevacizumab injections for exudative age-related macular degeneration in the right eye, developed decreased vision 4 days after her last injection. She had trace anterior chamber cells and 1+ vitritis, consistent with a bevacizumab-associated uveitis. The patient improved on topical steroids and cycloplegics. Subsequently, her exudative age-related macular degeneration was treated with monthly ranibizumab injections. Optical coherence tomography demonstrated persistent subretinal fluid despite treatment. Seven days after her 11th ranibizumab injection, she developed sudden decreased vision, 2+ anterior chamber cell, and 4+ vitritis. Presumptive treatment for an exogenous bacterial endophthalmitis was given after a vitreous biopsy was performed, which demonstrated severe sterile infiltrates that were culture negative. All injections were stopped. Three months later, the subretinal fluid had disappeared, the vitritis has nearly resolved, but some intraretinal fluid persisted.

CONCLUSION: Acute noninfectious uveitis, a known risk following injection with either bevacizumab or ranibizumab, may develop sequentially in the same patient, suggesting the possibility of cross-sensitivity. Additionally, spontaneous anatomical improvement after uveitis from antibody-based vascular endothelial growth factor inhibition implies a suppressive immunomodulatory effect on vascular permeability or choroidal neovascularization. The availability of agents with alternative molecular structures, such as aflibercept, may permit additional insights into the complex relationship between choroidal neovascularization, vitritis, and innate and other immunologic processes.

PMID: 25383816 [PubMed - in process]

Retin Cases Brief Rep. 2014 Jul 9. [Epub ahead of print]

RECURRENT HEMATURIA IN A PATIENT WITH A PREVIOUSLY UNDIAGNOSED TRANSITIONAL CELL CARCINOMA OF THE RIGHT URETER AFTER INTRAVITREAL BEVACIZUMAB (AVASTIN) INJECTION: A CASE REPORT.

Lemor D, Lazar D, Mazzulla DA.

PURPOSE: To report a case of gross hematuria in a patient with previously undiagnosed urothelial carcinoma of the right ureter after intravitreal bevacizumab (Avastin) injections.

METHODS: In this case report and review of the literature, an 81-year-old woman presented with neovascular age-related macular degeneration in the left eye. She was treated with repeated intravitreal bevacizumab (Avastin) injections. After injection, she reported two episodes of gross hematuria. After disclosing this information to her ophthalmologist, bevacizumab treatment was suspended and the

hematuria resolved. Urological evaluation revealed no abnormalities. Approximately 1 year later, treatment with intravitreal bevacizumab was resumed. After three injections, she again reported gross hematuria. Urological evaluation at that time revealed a high-grade urothelial carcinoma of the right ureter. A right nephroureterectomy was performed, and bevacizumab treatment was resumed. She did not report any subsequent episodes of hematuria.

CONCLUSION: Hematuria has previously been reported with systemic administration of bevacizumab. However, hematuria after intravitreal injections of bevacizumab has not been reported and is most likely occurring as a result of the systemic absorption of the drug. Further investigation of the systemic effects of intravitreal bevacizumab may be warranted.

PMID: 25383854 [PubMed - as supplied by publisher]

Am J Ther. 2014 Nov 13. [Epub ahead of print]

Aortoduodenal Fistula in a Patient on Intravitreal Bevacizumab Injections: A Case Report.

Pepper AN, Valenzuela MO, Oller KL.

Abstract: An 88-year-old woman on long-term intravitreal bevacizumab presented with acute gastrointestinal hemorrhage. She was stabilized and underwent nonrevealing upper endoscopy. She continued to require intermittent blood transfusions, and resulting computed tomography of the abdomen revealed an aortoduodenal fistula. The patient was undergoing treatment for her macular degeneration with intravitreal bevacizumab, an angiogenesis inhibitor frequently used to treat solid organ malignancies. Systemic administration has been associated with serious adverse events, including gastrointestinal hemorrhage, perforation, and fistula formation. Intravitreal bevacizumab has been used off-label to treat macular degeneration, but data on the safety of this therapy are limited. Given her lack of other risk factors, the authors postulate a potential association between intravitreal bevacizumab and aortoduodenal fistula formation in this patient.

PMID: 25397588 [PubMed - as supplied by publisher]

Ophthalmic Epidemiol. 2014 Dec;21(6):345-6.

Does Genetic Variation Influence Response to Treatment with Vascular Endothelial Growth Factor Inhibitors in Neovascular Age-related Macular Degeneration?

Chakravarthy U, Hagstrom SA.

PMID: 25387353 [PubMed - in process]

Other treatment & diagnosis

FASEB J. 2014 Nov 12. [Epub ahead of print]

Nanosecond laser therapy reverses pathologic and molecular changes in age-related macular degeneration without retinal damage.

Jobling AI, Guymer RH, Vessey KA, Greferath U, Mills SA, Brassington KH, Luu CD, Aung KZ, Trogrlic L, Plunkett M, Fletcher EL.

Abstract: Age-related macular degeneration (AMD) is a leading cause of vision loss, characterized by drusen deposits and thickened Bruch's membrane (BM). This study details the capacity of nanosecond

laser treatment to reduce drusen and thin BM while maintaining retinal structure. Fifty patients with AMD had a single nanosecond laser treatment session and after 2 yr, change in drusen area was compared with an untreated cohort of patients. The retinal effect of the laser was determined in human and mouse eyes using immunohistochemistry and compared with untreated eyes. In a mouse with thickened BM (ApoE null), the effect of laser treatment was quantified using electron microscopy and quantitative PCR. In patients with AMD, nanosecond laser treatment reduced drusen load at 2 yr. Retinal structure was not compromised in human and mouse retina after laser treatment, with only a discrete retinal pigment epithelium (RPE) injury, and limited mononuclear cell response observed. BM was thinned in the ApoE null mouse 3 mo after treatment (ApoE null treated 683 ± 38 nm, ApoE null untreated 890 ± 60 nm, C57Bl6J 606 ± 43 nm), with the expression of matrix metalloproteinase-2 and -3 increased ($>260\%$). Nanosecond laser resolved drusen independent of retinal damage and improved BM structure, suggesting this treatment has the potential to reduce AMD progression.

PMID: 25392267 [PubMed - as supplied by publisher]

Med Sci Monit. 2014 Nov 11;20:2243-9.

Ophthalmological features of Parkinson disease.

Nowacka B, Lubinski W, Honczarenko K, Potemkowski A, Safranow K.

Background: The aim of this study was to determine the type and frequency of ophthalmologic changes occurring in patients with Parkinson disease (PD).

Material and Methods: One hundred consecutive patients (196 eyes) with idiopathic PD and a control group consisting of 100 healthy patients (196 eyes) matched for age and sex underwent a complete ophthalmological examination of both eyes, including assessment of patient medical history, dry eye questionnaire, and visual hallucinations questionnaire, distance and near best corrected visual acuity (DBCVA, NBCVA), color vision, distance photopic contrast sensitivity, near point of convergence, slit lamp examination of the eye anterior segment, tear film osmolarity and breakup time, aqueous tear production, and intraocular pressure, as well as fundus examination and evaluation of the perimacular retinal thickness (RT) and peripapillary retinal nerve fiber layer (RNFL) thickness.

Results: In the eyes of PD patients DBCVA, NBCVA, contrast sensitivity, and color discrimination were significantly reduced. We also detected increased frequency of convergence insufficiency, seborrheic blepharitis, meibomian gland disease (MGD), dry eye syndrome, nuclear and posterior subcapsular cataract, and glaucoma ($p < 0.05$). However, intraocular pressure (IOP) was significantly lower in the PD group compared to controls. The frequency of visual hallucinations, age-related macular degeneration (ARMD), and other ophthalmological diseases, as well as RT and RNFL thickness, did not significantly differ between investigated groups.

Conclusions: Clinicians need to be aware of the association between PD and ophthalmological changes. Restoration of good-quality vision has a great impact on PD patients' quality of life, reduction of costs of treatment and care, and rehabilitation.

PMID: 25387009 [PubMed - in process]

Pathogenesis

Select item 2539036036.

Biomacromolecules. 2014 Nov 12. [Epub ahead of print]

Multifunctional PEG Retinylamine Conjugate Provides Prolonged Protection against Retinal Degeneration

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in Mice.

Yu G, Wu X, Ayat N, Maeda A, Gao SQ, Golczak M, Palczewski K, Lu ZR.

Abstract: A polyethylene glycol (PEG) retinylamine (Ret-NH₂) conjugate PEG-GFL-NH-Ret with a glycine-phenylalanine-leucine (GFL) spacer was synthesized for controlled oral delivery of Ret-NH₂ to treat retinal degenerative diseases, including Stargardt disease (STGD) and age-related macular degeneration (AMD). The peptide spacer was introduced for sustained release of the drug by digestive enzymes in the gastrointestinal tract. The pharmacokinetics experiments showed that the PEG conjugate could control the sustained drug release after oral administration and had much lower non-specific liver drug accumulation than the free drug in wild-type female C57BL mice. At the mean time, the conjugate maintained the same concentration of Ret-NH₂ in the eye as the free drug. Also, PEG-GFL-NH-Ret at a Ret-NH₂ equivalent dose of 25 mg/kg produced complete protection of Abca4^{-/-}Rdh8^{-/-} mouse retinas against light-induced retinal degeneration for at 3 days after oral administration as revealed by OCT retina imaging, whereas free Ret-NH₂ did not provide any protection under identical conditions. The polymer conjugate PEG-GFL-NH-Ret has great potential for controlled delivery of Ret-NH₂ to the eye for effective protection against retinal degenerative diseases.

PMID: 25390360 [PubMed - as supplied by publisher]

Int J Mol Med. 2014 Nov 10. [Epub ahead of print]

Subretinal injection of amyloid- β peptide accelerates RPE cell senescence and retinal degeneration.

Liu C, Cao L, Yang S, Xu L, Liu P, Wang F, Xu D.

Abstract: Drusen are considered a hallmark characteristic of age-related macular degeneration (AMD). In our previous study, we found that amyloid- β (A β) peptide, a component of drusen, induced the cells of the retinal pigment epithelium (RPE; RPE cells) to enter senescence; however, its effects in vivo remain unknown. Thus, the present study was carried out to explore the in vivo effects of A β peptide on RPE cell senescence and senescence-associated inflammation in C57BL/6 mice. C57BL/6 mice received a subretinal injection of A β (1-42) peptide; on day 7 post-injection, the mice were anesthetized and subjected to whole-body perfusion with 4% paraformaldehyde (PFA) in PBS and the whole eyes were then enucleated. Retinal function was assessed by electroretinography (ERG), and the morphological characteristics of the retina were examined by light and electron microscopy. Fundus autofluorescence (FAF) was examined by confocal scanning laser ophthalmoscopy (cSLO). The expression of p16INK4a, a marker of cellular senescence, was examined by immunofluorescence staining and western blot analysis. The RPE-choroid was analyzed for cytokine expression by RT-PCR. In A β (1-42)-injected mice, scotopic ERG responses declined. Degenerative alterations, including the disruption of the inner segment (IS)/outer segment (OS) junction and extensive vacuolation and thickness of Bruch's membrane (BrM) were observed under a light microscope. The accumulation of vacuoles and the loss of basal infoldings in the RPE were identified using an electron microscope. FAF and p16INK4a expression increased in A β (1-42)-injected mice. In addition, A β (1-42) upregulated interleukin (IL)-6 and IL-8 gene expression in the RPE-choroid. In conclusion, our results confirm the effects of A β (1-42) peptide on RPE senescence in vivo. The A β -injected mice developed AMD-like ocular pathology. It is thus suggested that RPE cell senescence is a potential mechanistic link between inflammation and retinal degeneration.

PMID: 25385658 [PubMed - as supplied by publisher]

Proc Natl Acad Sci U S A. 2014 Nov 10. [Epub ahead of print]

Pharmacological protection of retinal pigmented epithelial cells by sulindac involves PPAR- α

Sur A, Kesaraju S, Prentice H, Ayyanathan K, Baronas-Lowell D, Zhu D, Hinton DR, Blanks J, Weissbach

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H.

Abstract: The retinal pigmented epithelial (RPE) layer is one of the major ocular tissues affected by oxidative stress and is known to play an important role in the etiology of age-related macular degeneration (AMD), the major cause of blinding in the elderly. In the present study, sulindac, a nonsteroidal antiinflammatory drug (NSAID), was tested for protection against oxidative stress-induced damage in an established RPE cell line (ARPE-19). Besides its established antiinflammatory activity, sulindac has previously been shown to protect cardiac tissue against ischemia/reperfusion damage, although the exact mechanism was not elucidated. As shown here, sulindac can also protect RPE cells from chemical oxidative damage or UV light by initiating a protective mechanism similar to what is observed in ischemic preconditioning (IPC) response. The mechanism of protection appears to be triggered by reactive oxygen species (ROS) and involves known IPC signaling components such as PKG and PKC epsilon in addition to the mitochondrial ATP-sensitive K⁺ channel. Sulindac induced iNOS and Hsp70, late-phase IPC markers in the RPE cells. A unique feature of the sulindac protective response is that it involves activation of the peroxisome proliferator-activated receptor alpha (PPAR- α). We have also used low-passage human fetal RPE and polarized primary fetal RPE cells to validate the basic observation that sulindac can protect retinal cells against oxidative stress. These findings indicate a mechanism for preventing oxidative stress in RPE cells and suggest that sulindac could be used therapeutically for slowing the progression of AMD.

PMID: 25385631 [PubMed - as supplied by publisher]

J Neurosci. 2014 Nov 12;34(46):15356-68.

The Transcription Factor GTF2IRD1 Regulates the Topology and Function of Photoreceptors by Modulating Photoreceptor Gene Expression across the Retina.

Masuda T, Zhang X, Berlinicke C, Wan J, Yerrabelli A, Conner EA, Kjellstrom S, Bush R, Thorgeirsson SS, Swaroop A, Chen S, Zack DJ.

Abstract: The mechanisms that specify photoreceptor cell-fate determination, especially as regards to short-wave-sensitive (S) versus medium-wave-sensitive (M) cone identity, and maintain their nature and function, are not fully understood. Here we report the importance of general transcription factor II-I repeat domain-containing protein 1 (GTF2IRD1) in maintaining M cone cell identity and function as well as rod function. In the mouse, GTF2IRD1 is expressed in cell-fate determined photoreceptors at postnatal day 10. GTF2IRD1 binds to enhancer and promoter regions in the mouse rhodopsin, M- and S-opsin genes, but regulates their expression differentially. Through interaction with the transcription factors CRX and thyroid hormone receptor β 2, it enhances M-opsin expression, whereas it suppresses S-opsin expression; and with CRX and NRL, it enhances rhodopsin expression. In an apparent paradox, although GTF2IRD1 is widely expressed in multiple cell types across the retina, knock-out of GTF2IRD1 alters the retinal expression of only a limited number of annotated genes. Interestingly, however, the null mutation leads to altered topology of cone opsin expression in the retina, with aberrant S-opsin overexpression and M-opsin underexpression in M cones. Gtf2ird1-null mice also demonstrate abnormal M cone and rod electrophysiological responses. These findings suggest an important role for GTF2IRD1 in regulating the level and topology of rod and cone gene expression, and in maintaining normal retinal function.

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Epidemiology

Invest Ophthalmol Vis Sci. 2014 Nov 11. [Epub ahead of print]

Physical activity and the 15-year incidence of age-related macular degeneration.

Gopinath B, Liew G, Burlutsky G, Mitchell P.

Purpose: There is uncertainty in the published literature as to whether physical activity should be advocated for age-related macular degeneration (AMD) prevention. We aimed to prospectively assess the association between physical activity and the 15-year incidence of AMD in older adults.

Methods: AMD was assessed from retinal photographs. Participants provided details of walking exercise and the performance of moderate or vigorous activities, which were used to calculate metabolic equivalents (METs).

Results: After adjusting for age, adults aged ≥ 75 years in the highest tertile (the most physically active) compared to those in the lowest tertile (least physically active) were 79% less likely to develop incident late AMD over the 15 years, odds ratio, OR, 0.21 (95% confidence intervals, CI, 0.05-0.95). However, after further adjusting for gender, body mass index, smoking, fish consumption and white cell count, this association was no longer statistically significant, OR 0.26 (95% CI 0.06-1.28). Significant associations were not found in those aged < 75 or with the 15-year cumulative incidence of early AMD

Conclusions: Physical activity did not influence the risk of AMD over 15 years in older adults, independent of diet, smoking, white cell count and body mass index.

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J Expo Sci Environ Epidemiol. 2014 Nov 12. [Epub ahead of print]

Cadmium exposure and age-related macular degeneration.

Kim MH, Zhao D, Cho J, Guallar E.

Abstract: Cadmium (Cd) has been proposed as a risk factor for age-related macular degeneration (AMD), but the association between Cd exposure and AMD risk in large population studies is unknown. This study evaluated the association of Cd exposure with AMD in a large representative sample of Korean men and women. This was a cross-sectional study of 3865 Korean adults ≥ 40 years of age who participated in the Korean National Health and Nutrition Examination Survey (KNHANES) during 2008-2011. Cd concentrations in whole blood were measured by graphite-furnace atomic absorption spectrometry. The presence of AMD was determined in digital non-mydratic fundus photographs. Cd levels were higher in participants with AMD compared with those without AMD (1.3 vs 1.1 $\mu\text{g/l}$, respectively, $P < 0.001$). In fully adjusted models, the odds ratio for AMD comparing the highest with the lowest Cd quartiles was 1.92 (95% CI=1.08-3.39; P for trend 0.029). In restricted cubic spline models, the association between Cd and AMD was approximately linear, with no evidence of threshold effects. Blood Cd concentrations were independently associated with the prevalence of AMD. If the association is proven causal, population-based preventive strategies to decrease Cd exposure could reduce the population burden of AMD. *Journal of Exposure Science and Environmental Epidemiology* advance online publication, 12 November 2014; doi:10.1038/jes.2014.75.

PMID: 25388812 [PubMed - as supplied by publisher]

Genetics

Sci Rep. 2014 Nov 12;4:7018.

Gender specific association of a complement component 3 polymorphism with polypoidal choroidal vasculopathy.

Liu K, Lai TY, Chiang SW, Chan VC, Young AL, Tam PO, Pang CP, Chen LJ.

Abstract: Neovascular age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) are leading causes of irreversible blindness in developed countries. In this study, we investigated the associations of haplotype-tagging single nucleotide polymorphisms (SNPs) in the complement component 3 (C3) gene with both neovascular AMD and PCV, and potential epistatic effects on C3. Eight tagging SNPs in C3 were genotyped in 708 unrelated study subjects: 200 neovascular AMD patients, 233 PCV patients and 275 controls. Among the eight C3 SNPs, rs17030 was associated with PCV after adjusted for gender and SNP-gender interaction ($P = 0.008$, OR = 2.94; 95% CI: 1.32-6.52). Moreover, an interaction between rs17030 and gender was identified in PCV ($P = 0.02$). After stratification by gender, the rs17030 G allele was found to confer an increased risk for PCV in male ($P = 0.010$, OR = 1.56) but not in female. The haplotype AG defined by the major alleles of rs17030 and rs344555 was also associated with PCV in male ($P = 0.010$, OR = 0.64). In contrast to PCV, none of the eight SNPs was significantly associated with neovascular AMD. This study shows an association of C3 rs17030 with PCV in male, indicating that C3 may have an epistatic effect with gender in the pathogenesis of PCV.

PMID: 25388911 [PubMed - in process]

Diet & lifestyle

PLoS One. 2014 Nov 13;9(11):e112682.

Zinc supplementation inhibits complement activation in age-related macular degeneration.

Smailhodzic D, van Asten F, Blom AM, Mohlin FC, den Hollander AI, van de Ven JP, van Huet RA, Groenewoud JM, Tian Y, Berendschot TT, Lechanteur YT, Fauser S, de Bruijn C, Daha MR, van der Wilt GJ, Hoyng CB, Klevering BJ.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the Western world. AMD is a multifactorial disorder but complement-mediated inflammation at the level of the retina plays a pivotal role. Oral zinc supplementation can reduce the progression of AMD but the precise mechanism of this protective effect is as yet unclear. We investigated whether zinc supplementation directly affects the degree of complement activation in AMD and whether there is a relation between serum complement catabolism during zinc administration and the complement factor H (CFH) gene or the Age-Related Maculopathy susceptibility 2 (ARMS2) genotype. In this open-label clinical study, 72 randomly selected AMD patients in various stages of AMD received a daily supplement of 50 mg zinc sulphate and 1 mg cupric sulphate for three months. Serum complement catabolism-defined as the C3d/C3 ratio-was measured at baseline, throughout the three months of supplementation and after discontinuation of zinc administration. Additionally, downstream inhibition of complement catabolism was evaluated by measurement of anaphylatoxin C5a. Furthermore, we investigated the effect of zinc on complement activation in vitro. AMD patients with high levels of complement catabolism at baseline exhibited a steeper decline in serum complement activation ($p < 0.001$) during the three month zinc supplementation period compared to patients with low complement levels. There was no significant association of change in complement catabolism and CFH and ARMS2 genotype. In vitro zinc sulphate directly inhibits complement catabolism in hemolytic assays and membrane attack complex (MAC) deposition on RPE cells. This study provides evidence that daily administration of 50 mg zinc sulphate can inhibit complement catabolism in AMD patients with increased complement activation. This could explain part of the mechanism by which zinc slows AMD progression.

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