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MD Research News

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

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Drug treatment

Ophthalmology. 2012 Apr 26. [Epub ahead of print]

Ranibizumab and Bevacizumab for Treatment of Neovascular Age-Related Macular Degeneration: Two-Year Results.

Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, Toth C, Redford M, Ferris FL 3rd; Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group( ) Writing Committee:.

Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio.

OBJECTIVE: To describe effects of ranibizumab and bevacizumab when administered monthly or as needed for 2 years and to describe the impact of switching to as-needed treatment after 1 year of monthly treatment.

DESIGN: Multicenter, randomized clinical trial.

PARTICIPANTS: Patients (n = 1107) who were followed up during year 2 among 1185 patients with neovascular age-related macular degeneration who were enrolled in the clinical trial.

INTERVENTIONS: At enrollment, patients were assigned to 4 treatment groups defined by drug (ranibizumab or bevacizumab) and dosing regimen (monthly or as needed). At 1 year, patients initially assigned to monthly treatment were reassigned randomly to monthly or as-needed treatment, without changing the drug assignment.

MAIN OUTCOME MEASURES: Mean change in visual acuity.

RESULTS: Among patients following the same regimen for 2 years, mean gain in visual acuity was similar for both drugs (bevacizumab-ranibizumab difference, -1.4 letters; 95% confidence interval [CI], -3.7 to 0.8; P = 0.21). Mean gain was greater for monthly than for as-needed treatment (difference, -2.4 letters; 95% CI, -4.8 to -0.1; P = 0.046). The proportion without fluid ranged from 13.9% in the bevacizumab-as-needed group to 45.5% in the ranibizumab monthly group (drug, P = 0.0003; regimen, P < 0.0001). Switching from monthly to as-needed treatment resulted in greater mean decrease in vision during year 2 (-2.2 letters; P = 0.03) and a lower proportion without fluid (-19%; P < 0.0001). Rates of death and arteriothrombotic events were similar for both drugs (P > 0.60). The proportion of patients with 1 or more systemic serious adverse events was higher with bevacizumab than ranibizumab (39.9% vs. 31.7%; adjusted risk ratio, 1.30; 95% CI, 1.07-1.57; P = 0.009). Most of the excess events have not been associated previously with systemic therapy targeting vascular endothelial growth factor (VEGF).

CONCLUSIONS: Ranibizumab and bevacizumab had similar effects on visual acuity over a 2-year period. Treatment as needed resulted in less gain in visual acuity, whether instituted at enrollment or after 1 year of monthly treatment. There were no differences between drugs in rates of death or arteriothrombotic events. The interpretation of the persistence of higher rates of serious adverse events with bevacizumab is uncertain because of the lack of specificity to conditions associated with inhibition of VEGF.

PMID: 22555112 [PubMed - as supplied by publisher]

BMJ. 2012 May 1;344:e2941. doi: 10.1136/bmj.e2941.

Implications of "not me" drugs for health systems: lessons from age related macular degeneration.

Campbell RJ, Dhalla IA, Gill SS, Bell CM.

Department of Ophthalmology, Hotel Dieu Hospital and Queen's University, 166 Brock Street, Kingston, Ontario, Canada K7L 5G2.

PMID: 22549055 [PubMed - in process]

Ophthalmology. 2012 May 1. [Epub ahead of print]

Subfoveal Choroidal Thickness after Ranibizumab Therapy for Neovascular Age-related Macular Degeneration: 12-Month Results.

Yamazaki T, Koizumi H, Yamagishi T, Kinoshita S.

Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan.

PURPOSE: To investigate the changes in subfoveal choroidal thickness after intravitreal injections of ranibizumab (IVRs) for neovascular age-related macular degeneration (AMD).

DESIGN: Prospective, consecutive, interventional case series.

PARTICIPANTS: Eighty eyes (40 affected eyes with neovascular AMD and 40 unaffected fellow eyes) of 40 patients.

METHODS: Forty eyes with neovascular AMD were treated with 0.5-mg IVRs monthly for 3 months and received additional IVRs as needed over the following 9-month period. Subfoveal choroidal thickness in all 80 eyes was measured by use of enhanced depth imaging optical coherence tomography images before and after starting the IVRs.

MAIN OUTCOME MEASURES: Changes in subfoveal choroidal thickness after treatment by IVRs over a 12-month period.

RESULTS: Twenty-three eyes (57.5%) were diagnosed with typical neovascular AMD, 16 eyes (40%) were diagnosed with polypoidal choroidal vasculopathy, and 1 eye (2.5%) was diagnosed with retinal angiomatous proliferation. Fifteen eyes (38%) had received some previous treatments for the neovascular lesion before undergoing the IVRs. The mean best-corrected visual acuity of the affected eyes was improved from 0.54 logarithm of the minimum angle of resolution units at baseline to 0.42 at 12 months ($P = 0.020$). The mean subfoveal choroidal thickness in the affected eyes decreased from 244±62 μm at baseline to 234±66 μm at 1 month ($P = 0.013$), 226±68 μm at 3 months ($P<0.001$), 229±67 μm at 6 months ($P = 0.002$), and 226±66 μm at 12 months ($P = 0.002$; the change ratio, 93%), whereas that in the unaffected eyes changed from 237±80 μm at baseline to 238±83 μm at 12 months ($P = 0.78$). In the affected eyes, the change ratio of subfoveal choroidal thickness at 12 months was not correlated with the number of IVRs (mean, 5.8±2.9). Subfoveal choroidal thickness demonstrated a similar trend toward

decreasing during the following period independent of the subtypes of neovascular AMD or the treatment histories.

CONCLUSIONS: Subfoveal choroidal thickness decreased after IVRs in eyes with neovascular AMD. Intravitreal injections of ranibizumab may provide a pharmacologic effect not only on the neovascular lesion but also on the underlying choroid.

PMID: 22551738 [PubMed - as supplied by publisher]

Arq Bras Oftalmol. 2012 Feb;75(1):71-6.

New approaches and potential treatments for dry age-related macular degeneration.

Damico FM, Gasparin F, Scolari MR, Pedral LS, Takahashi BS.

Medical School, University of São Paulo, São Paulo, SP, Brazil.

Abstract

Emerging treatments for dry age-related macular degeneration (AMD) and geographi c atrophy focus on two strategies that target components involved in physiopathological pathways: prevention of photoreceptors and retinal pigment epithelium loss (neuroprotection induction, oxidative damage prevention, and visual cycle modification) and suppression of inflammation. Neuroprotective drugs, such as ciliary neurotrophic factor, brimonidine tartrate, tandospirone, and anti-amyloid β antibodies, aim to prevent apoptosis of retinal cells. Oxidative stress and depletion of essential micronutrients are targeted by the Age-Related Eye Disease Study (AREDS) formulation. Visual cycle modulators reduce the activity of the photoreceptors and retinal accumulation of toxic fluorophores and lipofuscin. Eyes with dry age-related macular degeneration present chronic inflammation and potential treatments include corticosteroid and complement inhibition. We review the current concepts and rationale of dry age-related macular degeneration treatment that will most likely include a combination of drugs targeting different pathways involved in the development and progression of age-related macular degeneration.

PMID: 22552424 [PubMed - in process]

Retina. 2012 Mar 23. [Epub ahead of print]

COMBINED INTRAVITREAL RANIBIZUMAB AND PHOTODYNAMIC THERAPY FOR POLYPOIDAL CHOROIDAL VASCULOPATHY.

Saito M, Iida T, Kano M.

Department of Ophthalmology, Fukushima Medical University School of Medicine, Fukushima, Japan.

PURPOSE: To clarify the efficacy of combined therapy with intravitreal ranibizumab injections and photodynamic therapy in patients with symptomatic polypoidal choroidal vasculopathy.

METHODS: We retrospectively reviewed 28 naive eyes of 28 patients (17 men, 11 women; mean age, 73.4 years; range, 55-85 years) with 20/40 or less baseline visual acuity treated with 3 consecutive monthly intravitreal injections of ranibizumab (0.5 mg/0.05 mL) and photodynamic therapy and followed-up for at least 12 months. Photodynamic therapy was administered 1 day or 2 days after the initial injection of ranibizumab.

RESULTS: The mean best-corrected visual acuity levels significantly ($P < 0.0001$) improved from 0.33 at baseline to 0.61 at 12 months. The mean improvement in best-corrected visual acuity 12 months from baseline was 2.65 lines. The best-corrected visual acuity at 12 months improved in 15 eyes (53.6%) by ≥3

lines and was stable (defined as a loss of <3 lines of vision) in 13 eyes (46.4%). The central retinal thickness significantly (P < 0.0001) decreased from 366 µm to 151 µm at 12 months. The mean numbers of photodynamic therapy treatments and injections during 12 months including the treatments during the initial regimen were 1.1 and 3.7, respectively. No complications developed.

CONCLUSION: Combined intravitreal ranibizumab and photodynamic therapy for polypoidal choroidal vasculopathy maintained or improved visual acuity and reduced the exudation without adverse events.

PMID: 22547209 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2012 May;87(5):153-156. Epub 2012 Mar 19.

Choroidal neovascularization secondary to pseudoxanthoma elasticum treated with ranibizumab: a report of 2 cases.

[Article in English, Spanish]

González-Gómez A, Morillo MJ, González-Escobar AB, García-Campos JM.

Servicio de Oftalmología, Hospital Universitario Virgen de la Victoria, Málaga, España.

CASE REPORT: We report 2 cases of pseudoxanthoma elasticum with angioid streaks and choroidal neovascularization (CNV) in both eyes. Intravitreal ranibizumab (Lucentis) was administered with successful results in both cases. DISCUSSION: CNV has been reported to occur in 72% to 86% of patients with angioid streaks. Although uncommon, the impact of CNV is important because it tends to affect people of working age. Based on the effectiveness of ranibizumab in other secondary CNVs, we decided to use it in our patients, observing the functional and anatomical improvement.

PMID: 22554559 [PubMed - as supplied by publisher]

Vestn Ross Akad Med Nauk. 2012;(1):61-5.

[Modern aspects of diabetic retinopathy and diabetic macular oedema treatment].

[Article in Russian]

[No authors listed]

Abstract

Main reasons of eyesight deterioration in diabetic patients are diabetic retinopathy (DR) and diabetic macular oedema (DMO). International multicenter studies have shown that retinal laser coagulation in the event of DMO decreases the risk of eyesight loss in 50%, though only in 16% patients it was also possible to improve their eyesight. Use of vascular endothelial growth factor inhibitor--Ranibizumab--have opened a new era in DMA treatment. It's efficacy and safety have been proven in several international studies. This article contains our own data upon the use of Lucentis in patients with DMO. Intravitreal Luzentis injections and subsequent retinal lasercoagulation in the macular zone were performed on 43 eyes; follow up period--6 months. Additional injections were required in 19 cases, average amount of injections--1,4. Mean corrected visual acuity before the treatment was 0,37 +/- 0,06, after 7 days, 1, 3 and 6 months. - respectively 0,41 +/- 0,06, 0,49 +/- 0,06, 0,51 +/- 0,07 and 0,52 +/- 0,07($p<0,05$). Mean retina thickness in central zone was 428 +/- 125 mkm before treatment, 391 +/- 24 mkm 7 days after the last injection 349 +/- 23, 313 +/- 21 and 308 +/- 20 mkm ($p<0,05$) after 1, 3 and 6 months. In addition to that Luzentis use in preoperative period in patients with non-complicated proliferative DR allowed to decrease the risk of hemorrhagic complications. Thereby, intravitreal injections of Luzentis improve functional result of treatment of patients with DMO, increase efficacy and safety of surgical interventions in patients with complicated

forms of proliferating DR.

PMID: 22550713 [PubMed - in process]

Arch Soc Esp Oftalmol. 2012 May;87(5):149-152. Epub 2012 Feb 9.

Intravitreal ranibizumab for choroidal neovascularisation associated with adult-onset vitelliform dystrophy.

[Article in English, Spanish]

Prieto-Calvo E, Torrón-Fernández Blanco C, Egea-Estopiñán C, Güerri-Monclús N, Ferrer-Novella E, Ruiz-Moreno O, Pablo-Julvez LE.

Servicio de Oftalmología, Hospital Universitario Miguel Servet, Zaragoza, España.

Abstract

CASE REPORT: A 70-year-old male patient diagnosed with bilateral adult-onset vitelliform dystrophy presented with a sudden decrease of vision in his left eye associated with the appearance of an occult type of neovascular membrane. It was treated with intravitreal ranibizumab due to juxtafoveal location of the membrane. Two injections were needed to induce total regression of the lesion. DISCUSSION: Intravitreal ranibizumab may be effective to induce morphological and functional improvement in cases of choroidal neovascularization secondary to adult-onset vitelliform foveomacular dystrophy. Further case series are required to confirm this observation.

PMID: 22554558 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Bull Soc Belge Ophtalmol. 2012;(319):75-83.

Oximetry: recent insights into retinal vasopathies and glaucoma.

Boeckaert J, Vandewalle E, Stalmans I.

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Abstract

This review will highlight a new technology and recent insights into measuring retinal oxygen saturation in several ophthalmic diseases. A growing body of evidence suggests that disturbances in retinal blood flow and oxygenation are related to several retinopathies and glaucoma, which can severely impair vision. The retinal oximeter may allow researchers and physicians to gain deeper insights into retinal physiology and clarify the impact of ischemia on retinal health and function. There are two commercially available systems to measure retinal oxygen saturation: the Oxymap retinal oximeter (Reykjavik, Iceland) and the Imedos Systems UG (Jena, Germany). In this review we will focus on the results obtained with Oxymap. Direct and non-invasive measurement of retinal oxygen saturation have potentially useful diagnostic and therapeutic indications in various eye diseases such as diabetic retinopathy, age-related macular degeneration, central retinal vein and artery occlusion, anterior ischemic optic neuropathy and retinopathy of prematurity. Despite several limitations, oxygen saturation assessment in the retinal vessels is a significant advancement in the understanding of ocular diseases. Nevertheless, further studies are needed to validate the use of oximetry in retinal vasopathies and glaucoma.

PMID: 22550781 [PubMed - in process]

Am J Occup Ther. 2012 May-Jun;66(3):277-83.

Systematic review of occupation- and activity-based health management and maintenance interventions for community-dwelling older adults.

Arbesman M, Mosley LJ.

Marian Arbesman, PhD, OTR/L, is Consultant, AOTA Evidence-Based Practice Project; President, ArbesIdeas, Inc., 19 Hopkins Road, Williamsville, NY 14221; and Adjunct Assistant Professor, Department of Rehabilitation Science, University at Buffalo, State University of New York, Williamsville; ma@ArbesIdeas.com.

Abstract

We describe the results of a systematic review of the literature on occupation- and activity-based health management and maintenance interventions for productive aging. We found moderate to strong evidence that client-centered occupational therapy improved physical functioning and occupational performance related to health management in community-dwelling older adults, as well as in adults with osteoarthritis and macular degeneration. We found moderate evidence that health education programs reduce pain and increase physical activity and that individualized health action plans improve activities of daily living function and participation in physical activities. The evidence that self-management programs result in a decrease in pain and disability and that incorporating cognitive-behavioral principles into physical activity improves long-term participation in exercise was also moderate. Although the evidence for skill-specific training in isolation is limited, effectiveness increases when skill-specific training is combined with health management programs. The implications for practice, education, and research are discussed.

PMID: 22549592 [PubMed - in process]

Retina. 2012 Apr 27. [Epub ahead of print]

COMPARISON OF COLOR FUNDUS PHOTOGRAPHS AND FUNDUS AUTOFLUORESCENCE IMAGES IN MEASURING GEOGRAPHIC ATROPHY AREA.

Khanifar AA, Lederer DE, Ghodasra JH, Stinnett SS, Lee JJ, Cousins SW, Bearelly S.

The Duke Center for Macular Diseases and Albert Eye Research Institute, Duke Eye Center, Durham, North Carolina.

PURPOSE: To assess the agreement between color fundus photographs (CFP) and fundus autofluorescence (FAF) images when measuring geographic atrophy (GA) area and reproducibility of measurements between graders. Frequency and disagreement types were also determined.

METHODS: Eyes with GA secondary to age-related macular degeneration had CFP and FAF imaging on the same day. Seventy-two eyes from 72 patients were included in the analysis. Three graders calculated GA area using digital imaging software. Main outcome measures included agreement between graders for GA area on both FAF and CFP and agreement between both imaging modalities.

RESULTS: The intraclass correlation for the 3 graders for FAF images was 0.99 (95% confidence interval, 0.98-0.99). For CFP, it was 0.96 (95% confidence interval, 0.94-0.97). The intraclass correlation between imaging modalities for Graders 1, 2, and 3 were 0.93, 0.85, and 0.87, respectively. Sensitivities to detect involvement of fovea (CFP, 86-97%; FAF, 72-93%) and specificities to detect sparing of fovea (CFP, 74-76%; FAF, 59-88%) overlapped between imaging modalities.

CONCLUSION: Both CFP and FAF imaging are reliable for measuring GA area. Interobserver agreement was slightly higher for FAF images. Although the high agreement between modalities suggests that either would be appropriate for measuring GA area, using both may be the best approach for following GA progression.

PMID: 22547167 [PubMed - as supplied by publisher]

Pathogenesis

Cell. 2012 Apr 26. [Epub ahead of print]

DICER1 Loss and Alu RNA Induce Age-Related Macular Degeneration via the NLRP3 Inflammasome and MyD88.

Tarallo V, Hirano Y, Gelfand BD, Dridi S, Kerur N, Kim Y, Cho WG, Kaneko H, Fowler BJ, Bogdanovich S, Albuquerque RJ, Hauswirth WW, Chiodo VA, Kugel JF, Goodrich JA, Ponicsan SL, Chaudhuri G, Murphy MP, Dunaief JL, Ambati BK, Ogura Y, Yoo JW, Lee DK, Provost P, Hinton DR, Núñez G, Baffi JZ, Kleinman ME, Ambati J.

Department of Ophthalmology & Visual Sciences, University of Kentucky, Lexington, KY 40506, USA.

Abstract

Alu RNA accumulation due to DICER1 deficiency in the retinal pigmented epithelium (RPE) is implicated in geographic atrophy (GA), an advanced form of age-related macular degeneration that causes blindness in millions of individuals. The mechanism of Alu RNA-induced cytotoxicity is unknown. Here we show that DICER1 deficit or Alu RNA exposure activates the NLRP3 inflammasome and triggers TLR-independent MyD88 signaling via IL18 in the RPE. Genetic or pharmacological inhibition of inflammasome components (NLRP3, Pycard, Caspase-1), MyD88, or IL18 prevents RPE degeneration induced by DICER1 loss or Alu RNA exposure. These findings, coupled with our observation that human GA RPE contains elevated amounts of NLRP3, PYCARD, and IL18 and evidence of increased Caspase-1 and MyD88 activation, provide a rationale for targeting this pathway in GA. Our findings also reveal a function of the inflammasome outside the immune system and an immunomodulatory action of mobile elements.

PMID: 22541070 [PubMed - as supplied by publisher]

Mol Aspects Med. 2012 Apr 21. [Epub ahead of print]

Understanding age-related macular degeneration (AMD): Relationships between the photoreceptor/retinal pigment epithelium/Bruch's membrane/choriocapillaris complex.

Bhutto I, Lutty G.

Wilmer Ophthalmological Institute, Johns Hopkins Hospital, Baltimore, MD, United States.

Abstract

There is a mutualistic symbiotic relationship between the components of the photoreceptor/retinal pigment epithelium (RPE)/Bruch's membrane (BrMb)/choriocapillaris (CC) complex that is lost in AMD. Which component in the photoreceptor/RPE/BrMb/CC complex is affected first appears to depend on the type of AMD. In atrophic AMD (~85-90% of cases), it appears that large confluent drusen formation and hyperpigmentation (presumably dysfunction in RPE) are the initial insult and the resorption of these drusen and loss of RPE (hypopigmentation) can be predictive for progression of geographic atrophy (GA). The death and dysfunction of photoreceptors and CC appear to be secondary events to loss in RPE. In neovascular AMD (~10-15% of cases), the loss of choroidal vasculature may be the initial insult to the complex. Loss of CC with an intact RPE monolayer in wet AMD has been observed. This may be due to reduction in blood supply because of large vessel stenosis. Furthermore, the environment of the CC, basement membrane and intercapillary septa, is a proinflammatory milieu with accumulation of complement components as well as proinflammatory molecules like CRP during AMD. In this toxic milieu, CC die or become dysfunction making adjacent RPE hypoxic. These hypoxic cells then produce angiogenic substances like VEGF that stimulate growth of new vessels from CC, resulting in choroidal neovascularization (CNV). The loss of CC might also be a stimulus for drusen formation since the disposal system for retinal debris and exocytosed material from RPE would be limited. Ultimately, the

photoreceptors die of lack of nutrients, leakage of serum components from the neovascularization, and scar formation. Therefore, the mutualistic symbiotic relationship within the photoreceptor/RPE/BrMb/CC complex is lost in both forms of AMD. Loss of this functionally integrated relationship results in death and dysfunction of all of the components in the complex.

PMID: 22542780 [PubMed - as supplied by publisher]

Biochim Biophys Acta. 2012 Apr 19. [Epub ahead of print]

Protein-oxidized phospholipid interactions in cellular signaling for cell death: From biophysics to clinical correlations.

Kinnunen PK, Kaarniranta K, Mahalka AK.

Helsinki Biophysics and Biomembrane Group, Department of Biomedical Engineering and Computational Science, Aalto University, Espoo, Finland.

Abstract

Oxidative stress is associated with several major ailments. However, it is only recently that the developments in our molecular level understanding of the consequences of oxidative stress in modifying the chemical structures of biomolecules, lipids in particular, are beginning to open new emerging insights into the significance of oxidative stress in providing mechanistic insights into the etiologies of these diseases. In this brief review we will first discuss the role of lipid oxidation in controlling the membrane binding of cytochrome c, a key protein in the control of apoptosis. We then present an overview of the impact of oxidized phospholipids on the biophysical properties of lipid bilayers and continue to discuss, how these altered properties can account for the observed enhancement of formation of intermediate state oligomers by cytotoxic amyloid forming peptides associated with pathological conditions as well as host defense peptides of innate immunity. In the third part, we will discuss how the targeting of oxidized phospholipids by i) pathology associated peptides and ii) host defense peptides can readily explain the observed clinical correlations associating Alzheimer's and Parkinson's diseases with increased risk for type 2 diabetes and age-related macular degeneration, and the apparent protective effect of Alzheimer's and Parkinson's diseases from some cancers, as well as the inverse, apparent protection by cancer from Alzheimer's and Parkinson's diseases. This article is part of a Special Issue entitled: Oxidized phospholipids-Their properties and interactions with proteins.

PMID: 22542574 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2012 Apr 26. [Epub ahead of print]

Improvement of Photoreceptor Integrity and Associated Visual Outcome in Neovascular Age-Related Macular Degeneration.

Kim YM, Kim JH, Koh HJ.

The Institute of Vision Research, Department of Ophthalmology, Yonsei University College of Medicine, Seoul, Korea.

PURPOSE: To evaluate the association between improvement of photoreceptor integrity and visual acuity (VA) after anti-vascular endothelial growth factor (anti-VEGF) injections in neovascular age-related macular degeneration (AMD).

DESIGN: Retrospective, cross-sectional study.

METHODS: Eighty-seven eyes of 84 patients who were newly diagnosed with neovascular AMD and

treated with anti-VEGF injections were reviewed retrospectively. Using spectral-domain optical coherence tomography, the status of the inner segment/outer segment photoreceptor junction (IS/OS) was graded and classified into 3 groups at baseline and 1 and 2 months after 3 monthly injections. The proportion of the improved IS/OS line after treatment was analyzed and correlated with VA.

RESULTS: The number of eyes in the IS/OS+ group, representing disrupted IS/OS line less than 200 μm, was increased from 9 (10%) at baseline to 33 (38%) at 1 month. There was a significant difference in the ratio of IS/OS+ group between baseline and 1 month (P < .001). Those in the IS/OS± group, showing focal disrupted IS/OS line between 200 and 800 μm, decreased from 29 (33%) to 22 eyes (25%). Improvement of the IS/OS line at 1 month compared to baseline was noted in 43 eyes (49%) and correlated with better VA (P < .016). No increase of VA was observed in 44 eyes without definite improvement. There was no significant correlation between improvement of the IS/OS line and VA from 1 to 2 months.

CONCLUSIONS: Assessing the change of the photoreceptor integrity before and after treatment would be a useful indicator to predict initial response to treatment and visual prognosis in patients with neovascular AMD.

PMID: 22541932 [PubMed - as supplied by publisher]

Mol Aspects Med. 2012 Apr 19. [Epub ahead of print]

Complement dysregulation in AMD: RPE-Bruch's membrane-choroid.

Sparrow JR, Ueda K, Zhou J.

Abstract

The question as to why the macula of the retina is prone to an aging disease (age-related macular degeneration) remains unanswered. This unmet challenge has implications since AMD accounts for approximately 54% of blindness in the USA (Swaroop et al., 2009). While AMD has onset in the elder years, it likely develops over time. Genetic discovery to date has accounted for approximately 50% of the inheritable component of AMD. The polymorphism that has been most widely studied is the Y402H allele in the complement factor H gene. The implication of this genetic association is that in a subset of AMD cases, unregulated complement activation is permissive for AMD. Given that this gene variant results in an amino acid substitution, it is assumed that this change will have functional consequences although the precise mechanisms are still unknown. Genetic predisposition is not the only factor however, since in this complex disease there is substantial evidence that lifestyle factors such as diet and smoking contribute to risk. Here we provide an overview of current knowledge with respect to factors involved in AMD pathogenesis. Interwoven with these issues is a discussion of the significant role played by aging processes, some of which are unique to the retina and retinal pigment epithelium. One recurring theme is the potential for disease promotion by diverse types of oxidation products.

PMID: 22542573 [PubMed - as supplied by publisher]

Epidemiology

Bull Soc Belge Ophtalmol. 2012;(319):35-41.

[Prevalence and risk factors of age macular degeneration (AMD) in a Tunisian hospital population].

[Article in French]

El Matri L, Bouraoui R, Chebil A, Kort F, Limaiem R, Bouladi M, Mghaieth F.

Service d'ophtalmologie B, Institut Hédi Rais d'ophtalmologie de Tunis. leila.elmatri@ms.tn

PURPOSE: To describe the prevalence and the risk factors for the age related macular degeneration (AMD) in a Tunisian hospital population.

PATIENTS AND METHODS: A total of 2204 subjects 50 years of age and older were enrolled in a prospective study conducted between august 2004 and February 2009. Medical history was reviewed. Subjects underwent a complete ophthalmic examination, including best corrected visual acuity and slit lamp biomicroscopy with fundus examination. Fundus photography and fluorescein angiography were performed if clinical features of AMD were observed on fundus examination. Cases were classified in early and late stages of AMD.

RESULTS: The prevalence of late AMD was higher than early AMD. Significant risk factors are age, male gender, smoking, excessive sunlight exposure and poor consumption of fish. Cardiovascular disease, diabetes and dyslipimia were not significantly associated to a high prevalence of AMD.

CONCLUSION: AMD is a multifactorial disease. In our Tunisian hospital population, the prevalence of AMD was higher than in the Europeen population. It can be explained by genetic differences or risk factors. Age, cigarette smoking and sunlight exposure were associated with increasing prevalence of AMD in Tunisia.

PMID: 22550776 [PubMed - in process]

Ophthalmology. 2012 May 1. [Epub ahead of print]

Risk Factors for Conversion to Neovascular Age-related Macular Degeneration Based on Longitudinal Morphologic and Visual Acuity Data.

Friberg TR, Bilonick RA, Brennen PM.

UPMC Eye Center, University of Pittsburgh, Pittsburgh, Pennsylvania.

PURPOSE: To use longitudinal quantitative morphologic and visual acuity (VA) data to investigate the risk of choroidal neovascularization (CNV) event occurrence in eyes with dry age-related macular degeneration (AMD).

DESIGN: Prospective observational study.

PARTICIPANTS: A total of 513 participants (844 eyes) followed longitudinally in one center enrolled in the Age-Related Eye Disease Study (AREDS) or the Prophylactic Treatment of AMD Study (PTAMD).

METHODS: We assessed images of previously obtained fundus photographs for the presence of macular pigmentation, drusen area, and drusen distribution (number and size), and fellow eye CNV status at baseline. Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) at each visit and the age of each subject were obtained. We used a longitudinal logistic mixed-effects model with random intercepts fitted to event occurrences to assess risk on a per eye basis.

MAIN OUTCOME MEASURES: Odds ratios for CNV event.

RESULTS: Thirty-one subjects (6.0%) had events. Only VA changes over time and follow-up interval showed statistically significant effects. Several statistical models that included VA at the previous visit were used. In 2 models, 3 categories of VA were used: ≤75 letters, >75 and ≤85 letters, and >85 letters. Two categories were used for follow-up: ≤3 years versus >3 years or ≤1 year versus >1 year. In the first model with categorization at 3 years, a decrease in acuity from the >85 letter category to ≤75 letters increased the odds of CNV by 16.9 times (P = 0.022). In the model with categorization at 1 year, a decrease in acuity from the >85-letter category to ≤75 letters increased the odds of CNV by 21.4 times (P = 0.0175). Differences between the follow-up intervals were significant (P = 0.043) and indicated a more than 7-fold increase in the odds. Changes in morphologic features of the macula did not show significant effects.

CONCLUSIONS: A decrease in VA to ≤75 ETDRS letters in an eye with an initial ETDRS baseline acuity of

>85 letters increases the likelihood of CNV by approximately 20-fold. This likelihood also increases with aging.

PMID: 22551740 [PubMed - as supplied by publisher]

Genetics

PLoS One. 2012;7(4):e35255. Epub 2012 Apr 25.

Comprehensive analysis of copy number variation of genes at chromosome 1 and 10 Loci associated with late age related macular degeneration.

Cantsilieris S, White SJ, Richardson AJ, Guymer RH, Baird PN.

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Abstract

Copy Number Variants (CNVs) are now recognized as playing a significant role in complex disease etiology. Age-related macular degeneration (AMD) is the most common cause of irreversible vision loss in the western world. While a number of genes and environmental factors have been associated with both risk and protection in AMD, the role of CNVs has remained largely unexplored. We analyzed the two major AMD risk-associated regions on chromosome 1q32 and 10q26 for CNVs using Multiplex Ligation-dependant Probe Amplification. The analysis targeted nine genes in these two key regions, including the Complement Factor H (CFH) gene, the 5 CFH-related (CFHR) genes representing a known copy number "hotspot", the F13B gene as well as the ARMS2 and HTRA1 genes in 387 cases of late AMD and 327 controls. No copy number variation was detected at the ARMS2 and HTRA1 genes in the chromosome 10 region, nor for the CFH and F13B genes at the chromosome 1 region. However, significant association was identified for the CFHR3-1 deletion in AMD cases ($p=2.38\times10(-12)$) OR=0.31, CI-0.95 (0.23-0.44), for both neovascular disease (nAMD) ($p=8.3\times10(-9)$) OR=0.36 CI-0.95 (0.25-0.52) and geographic atrophy (GA) ($p=1.5\times10(-6)$) OR=0.36 CI-0.95 (0.25-0.52) compared to controls. In addition, a significant association with deletion of CFHR1-4 was identified only in patients who presented with bilateral GA (p=0.02) (OR=7.6 CI-0.95 1.38-41.8). This is the first report of a phenotype specific association of a CNV for a major subtype of AMD and potentially allows for pre-diagnostic identification of individuals most likely to proceed to this end stage of disease.

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Leucocyte telomere length in age-related macular degeneration.

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Purpose: To evaluate the association between telomere length and age-related macular degeneration (AMD).

Methods: Circulating leucocyte telomere length and the proportion of telomeres <5 kb were analysed in blood DNA samples taken from 121 patients with exudative AMD (83%), large drusen (14%) or central geographic atrophy (3%). Controls consisted of 77 age-matched subjects without AMD. The AMD status was assessed by a masked analysis of fundus photographs or angiographs. Telomere length was

measured by Southern blotting.

Results: Mean (SD) telomere length was 7.76 kb (0.68) in AMD patients and 7.83 (0.69) in controls (p = 0.485). The corresponding proportions of telomeres <5 kb were 10.60 (2.76) and 10.05 (2.64) (p = 0.197). In this material, there was no correlation between telomere length and age, gender or smoking status. There were no differences between the major AMD risk single-nucleotide polymorphisms (SNPs) of the CFH, HTRA1 or C3 genes, expect for somewhat longer telomeres in controls with the C3 risk SNP. There were no differences in telomere length between patients with drusen or exudative AMD.

Conclusions: Telomere length is not associated with exudative AMD or high-risk drusen.

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Altered Expression of CD46 and CD59 on Leukocytes in Neovascular Age-Related Macular Degeneration.

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PURPOSE: To investigate the expression of the complement regulatory proteins CD46, CD55, and CD59 on peripheral leukocytes in neovascular age-related macular degeneration (AMD).

DESIGN: Prospective, case-control study.

METHODS: Thirty-five unrelated patients with neovascular AMD and 30 control individuals were included in this case-control study. All participants were subjected to a structured interview and detailed imaging (autofluorescence, digital funduscopy, spectral-domain optical coherence tomography, and fluorescein and indocyanine green angiography in patients suspected of having neovascular AMD) was performed. Fresh ethylenediamine-tetraacetic acid blood was obtained and stained with monoclonal antibodies. Using flow cytometry, the percentage of CD14(+) monocytes, CD45(+) lymphocytes, and CD45(+) granulocytes positive for CD46, CD55, and CD59 was determined in patients with neovascular AMD and was compared with that of controls.

RESULTS: We found that the expression of CD46 and CD59 was significantly lower on CD14(+) monocytes in patients with neovascular AMD compared with controls (P = .0070). A significantly lower expression of CD46 on lymphocytes was observed in patients with fibrosis compared with patients without fibrosis (P = .010).

CONCLUSIONS: Our study suggests that neovascular AMD is associated with an inadequate regulation of the complement system, supporting current evidence on the role of complement dysregulation in the pathogenesis of AMD.

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Characterization of an antibody that recognizes peptides containing D-β-aspartyl residues.

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PURPOSE: Biologically uncommon D-β-aspartyl (D-β-Asp) residues have been detected in proteins from various human tissues from elderly donors and are connected with cataract, age-related macular degeneration, Alzheimer disease and UV-irradiated skin. In a previous study, we prepared a highly specific antibody against the peptide Gly-Leu-D-β-Asp-Ala-Thr-Gly-Leu-D-β-Asp-Ala-Thr-Gly-Leu-D-β-Asp-Ala-Thr (designated peptide 3R) that corresponds to three repeats of positions 149-153 of human lens αA-crystallin. This antibody clearly distinguishes between the different configurations of the Asp residue in that it reacted strongly with the D-β-Asp-containing peptides but did not react with L-α-Asp-, L-β-Asp-, or D-α-Asp-containing peptides. However, it remains unclear whether the antibody recognizes the amino acid sequences surrounding the D-β-Asp residue. The purpose of the present study is to elucidate the sequence dependency of the epitope of the antigen.

METHODS: To clarify the properties of the anti-peptide 3R antibody, we used F-moc (9-fluorenylmethoxycarbonyl) solid phase chemistry to synthesize various peptides and analogs based on the peptides T18 (I(146)QTGLDATHAER(157)) and T6 (T(55)VLDAGISEVR(65)) which correspond to amino acid sequences 146-157 and 55-65, respectively of human αA-crystallin. The specificity of antibody was confirmed by ELISA (enzyme-linked immunosorbent assay) using these peptides.

RESULTS: The anti peptide 3R antibody specifically recognized D-β-Asp residues and does not react with other configurations of Asp such as the L-α, L-β, D-α isomers in peptides. When the Ala in the peptide was replaced by other amino acid residues, the antibody did not react with the antigen. The antibody requires the sequence Leu-D-β-Asp-Ala to detect D-β-Asp containing proteins in living tissue.

CONCLUSIONS: The anti peptide 3R antibody is a powerful and easy tool for detection of D-β-Asp containing proteins in living tissues from patients with age-related diseases. However, to detect the D-β-Asp containing proteins in the living tissues using the anti-peptide 3R antibody, the protein must contain the sequence Leu-D-β-Asp-Ala.

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Differential modulation of retinal degeneration by ccl2 and cx3cr1 chemokine signalling.

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Abstract

Microglia and macrophages are recruited to sites of retinal degeneration where local cytokines and chemokines determine protective or neurotoxic microglia responses. Defining the role of Ccl2-Ccr2 and Cx3cl1-Cx3cr1 signalling for retinal pathology is of particular interest because of its potential role in age-related macular degeneration (AMD). Ccl2, Ccr2, and Cx3cr1 signalling defects impair macrophage trafficking, but have, in several conflicting studies, been reported to show different degrees of age-related retinal degeneration. Ccl2/Cx3cr1 double knockout (CCDKO) mice show an early onset retinal degeneration and have been suggested as a model for AMD. In order to understand phenotypic discrepancies in different chemokine knockout lines and to study how defects in Ccl2 and/or Cx3cr1 signalling contribute to the described early onset retinal degeneration, we defined primary and secondary pathological events in CCDKO mice. To control for genetic background variability, we compared the original phenotype with that of single Ccl2, Cx3cr1 and Ccl2/Cx3cr1 double knockout mice obtained from backcrosses of CCDKO with C57Bl/6 mice. We found that the primary pathological event in CCDKO mice develops in the inferior outer nuclear layer independently of light around postnatal day P14. RPE and vascular lesions develop secondarily with increasing penetrance with age and are clinically similar to retinal telangiectasia not to choroidal neovascularisation. Furthermore, we provide evidence that a third autosomal

recessive gene causes the degeneration in CCDKO mice and in all affected re-derived lines and subsequently demonstrated co-segregation of the naturally occurring RD8 mutation in the Crb1 gene. By comparing CCDKO mice with re-derived CCl2(-/-)/Crb1(Rd8/RD8), Cx3cr1(-/-)/Crb1(Rd8/RD8) and CCl2(-/-)/Cx3cr1(-/-)/Crb1(Rd8/RD8) mice, we observed a differential modulation of the retinal phenotype by genetic background and both chemokine signalling pathways. These findings indicate that CCDKO mice are not a model of AMD, but a model for an inherited retinal degeneration that is differentially modulated by Ccl2-Ccr2 and Cx3cl1-Cx3cr1 chemokine signalling.

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Retinal function and CFH-ARMS2 polymorphisms analysis: a pilot study in Italian AMD patients.

Capoluongo E, Concolino P, Piccardi M, Marangoni D, Mello E, Minnella AM, Savastano C, Fadda A, Zuppi C, Bisti S, Falsini B.

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Abstract

Two major susceptibility genes, complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2), have been implicated in age-related macular degeneration (AMD) pathogenesis. We analyzed the association between CFH rs1061170 and/or ARMS2 rs10490924 polymorphisms with central retinal function properties, as evaluated by focal electroretinogram (fERG). Forty early AMD patients, with preserved visual acuity and typical macular lesions, underwent fERG recording (in response to 41 Hz flicker stimuli presented to the central 18 degrees) and CFH/ARMS2 genotyping. Mean fERG amplitude and sensitivity decreased in patients carrying CFH rs1061170 polymorphism ($p < 0.01$), compared with wild type ones, although visual acuity and funduscopic features were similar across the 2 groups. No significant fERG phase changes were observed. No association was detected between ARMS2 (rs10490924) polymorphism and fERG parameters. Our findings indicate that CFH (rs1061170) polymorphism impacts significantly on retinal function in early AMD patients, and support the hypothesis that dysfunctional CFH might result in early retinal function loss due to a reduction in the immune antioxidant defense mechanism.

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Diet

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Introduction to the issue regarding research regarding age related macular degeneration.

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