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MD Research News

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Drug treatment

J Pharm Biomed Anal. 2011 Jan 5. [Epub ahead of print]

Effective electrophoretic mobilities and charges of anti-VEGF proteins determined by capillary zone electrophoresis.

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Abstract

Macromolecules such as therapeutic proteins currently serve an important role in the treatment of eye diseases such as wet age-related macular degeneration and diabetic retinopathy. Particularly, bevacizumab and ranibizumab have been shown to be effective in the treatment of these diseases. Iontophoresis can be employed to enhance ocular delivery of these macromolecules, but the lack of information on the properties of these macromolecules has hindered its development. The objectives of the present study were to determine the effective electrophoretic mobilities and charges of bevacizumab, ranibizumab, and model compound polystyrene sulfonate (PSS) using capillary zone electrophoresis. Salicylate, lidocaine, and bovine serum albumin (BSA), which have known electrophoretic mobilities in the literature, were also studied to validate the present technique. The hydrodynamic radii and diffusion coefficients of BSA, bevacizumab, ranibizumab, and PSS were measured by dynamic light scattering. The effective charges were calculated using the Einstein relation between diffusion coefficient and electrophoretic mobility and the Henry equation. The results show that bevacizumab and ranibizumab have low electrophoretic mobilities and are net negatively charged in phosphate buffered saline (PBS) of pH 7.4 and 0.16M ionic strength. PSS has high negative charge but the electrophoretic mobility in PBS is lower than that expected from the polymer structure. The present study demonstrated that capillary electrophoresis could be used to characterize the mobility and charge properties of drug candidates in the development of iontophoretic drug delivery.

PMID: 21269789 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2011 Jan 23. [Epub ahead of print]

Qualitative Spectral OCT/SLO Analysis of Drusen Change in Dry Age-Related Macular Degeneration Patients Treated with Copaxone.

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Purpose: High-resolution spectral domain OCT/SLO (SD-OCT) has become an increasingly useful tool for differentiating drusen morphologic parameters such as shape, internal reflectivity, homogeneity, and presence of overlying hyperreflective foci. Our purpose was to evaluate which types of drusen may respond to Copaxone (glatiramer acetate) treatment of dry age-related macular degeneration (AMD) patients by shrinking or disappearing.

Methods: A prospective and interventional clinical trial of patients with dry AMD who received subcutaneous treatment with Copaxone or sham injections was conducted. SD-OCT images were used for analysis of drusen ultrastructure. Morphologic characteristics for specific drusen within the macular region were assessed with serial studies. Pre- and posttreatment statuses of drusen were compared. Main outcome measure was a change of drusen morphologic parameters in Copaxone-treated and sham-treated dry AMD patients between baseline and 12 weeks of treatment.

Results: Three hundred eleven drusen from 26 eyes of 14 dry AMD patients were evaluated. One hundred seventy-two drusen from 14 eyes (7 patients) of Copaxone-treated and 139 drusen from 12 eyes sham-treated (7 patients) were included. Overall, between baseline and 12-week visit, the percentage of drusen that disappeared/shrank in the Copaxone-treated group was 19.2% versus 6.5% in the sham-treated group (P = 0.13). The percentage of convex drusen that shrank or disappeared after 12 weeks of treatment was significantly higher in the Copaxone-treated group (27.8%) in comparison with the sham-treated group (6.8%) (P = 0.008). The difference between the groups was found to be statistically significant for drusen with low and medium internal reflectivity (P = 0.019 and P = 0.036, respectively).

Conclusions: Convex shape and low/medium internal reflectivity were found to be favorable parameters in prediction of drusen reduction in the Copaxone-treated patients. This study represents a preliminary attempt to identify SD-OCT features of drusen that may predict susceptibility to Copaxone treatment and therefore help clinicians decide which patients to treat.

PMID: 21254921 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Med J Malaysia. 2010 Mar;65(1):36-40.

Serum uric acid levels and its association with age-related macular degeneration (ARMD).

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Abstract

To investigate the possible association between serum uric acid levels, serum C-Reactive Protein (CRP), and age-related macular degeneration (ARMD). A total 232 patients of the eye department at Hospital Tuanku Ja'afar, Negeri Sembilan, Malaysia were recruited over 9 weeks. Participants were divided into ARMD (Non-Neovascular ARMD, and Neovascular ARMD) and control groups. 107 participants with non-neovascular ARMD, 6 with neovascular ARMD, and 119 controls participated in the study. The control patients had a similar average Serum Uric Acid level to the average of all patients with ARMD (P = 0.617). Control group: mean 299.19 micromol/l +/- std dev. 89.847 micromol/l. ARMD group: mean 302.53 micromol/l +/- std dev. 80.794 micromol/l. The average serum uric acid levels were higher in patients with neovascular ARMD (median = 397 mean +/- std dev = 389.67 +/- 38 micromol/l) than in the non-neovascular ARMD group (288.5 micromol/l, 297.86 +/- 80.26 micromol/l), and control group (295.5 micromol/l, 299.19 +/- 89.95 micromol/l). Comparing the standardised serum uric acid levels in the control group (Median = 0.5) against the two ARMD groups separately, there was no significant difference to the non-neovascular group (P = 0.448) but there was a difference significant to the neovascular ARMD group

(P = 0.044). The neovascular and non-neovascular ARMD groups had median CRP value of 0.25 mg/l and were not significantly different. There is no association between serum uric acid levels and ARMD as a whole. There is potentially an association between serum uric acid and neovascular ARMD, an association needs to be established further. There is no association between serum CRP and ARMD.

PMID: 21265246 [PubMed - in process]

Br J Ophthalmol. 2011 Jan 26. [Epub ahead of print]

Distinguishing wet from dry age-related macular degeneration using three-dimensional computer-automated threshold Amsler grid testing.

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Background/aims With the increased efficacy of current therapy for wet age-related macular degeneration (AMD), better ways to detect wet AMD are needed. This study was designed to test the ability of three-dimensional contrast threshold Amsler grid (3D-CTAG) testing to distinguish wet AMD from dry AMD.

Methods Conventional paper Amsler grid and 3D-CTAG tests were performed in 90 eyes: 63 with AMD (34 dry, 29 wet) and 27 controls. Qualitative comparisons were based upon the three-dimensional shapes of central visual field (VF) defects. Quantitative analyses considered the number and volume of the three-dimensional defects.

Results 25/34 (74%) dry AMD and 6/29 (21%) wet AMD eyes had no distortions on paper Amsler grid. Of these, 5/25 (20%) dry and 6/6 (100%) wet (p=0.03) AMD eyes exhibited central VF defects with 3D-CTAG. Wet AMD displayed stepped defects in 16/28 (57%) eyes, compared with only 2/34 (6%) of dry AMD eyes (p=0.002). All three volumetric indices of VF defects were two- to four-fold greater in wet than dry AMD (p<0.006). 3D-CTAG had 83.9% positive and 90.6% negative predictive values for wet AMD.

Conclusions 3D-CTAG has a higher likelihood of detecting central VF defects than conventional Amsler grid, especially in wet AMD. Wet AMD can be distinguished from dry AMD by qualitative and quantitative 3D-CTAG criteria. Thus, 3D-CTAG may be useful in screening for wet AMD, quantitating disease severity, and providing a quantitative outcome measure of therapy.

PMID: 21270434 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Jan 27. [Epub ahead of print]

Three-dimensional visualization of ocular vascular pathology by optical coherence angiography in vivo.

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Purpose: To demonstrate the clinical application of a noninvasive, three-dimensional vascular-imaging technique called "Doppler optical coherence angiography (OCA)". To evaluate the vascular architecture of polypoidal choroidal vasculopathy (PCV) using Doppler OCA.

Methods: We prospectively examined the eyes of 4 healthy subjects and 15 PCV patients. Three-dimensional vascular-flow imaging was performed using high-speed, high-resolution, and high-penetration spectral-domain Doppler optical coherence tomography. Two-dimensional images of the retina, choroid, and vascular lesions were obtained simultaneously.

Results: Distribution of blood flow detected by Doppler OCA imaging corresponded well with that by indocyanine angiographic imaging. PCV lesions were localized in the space between the retinal pigment epithelium and the Bruch's membrane.

Conclusions: Our findings using Doppler OCA indicated that PCV lesions have a similar architecture of choroidal neovascularization in age-related macular degeneration. Doppler OCA facilitates rapid and noninvasive examination of exudative macular diseases.

PMID: 21273541 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2011 Jan 26. [Epub ahead of print]

Spectral domain optical coherence tomography for higher precision in the evaluation of vitreoretinal adhesions in exudative age-related macular degeneration.

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Aim The role of changes at the vitreoretinal interface and vitreomacular traction forces in pathogenesis, and the course of exudative age-related macular degeneration (AMD) need further exploration. This study examines the localisation of adhesion and the direction of traction lines in eyes with exudative AMD.

Methods The cubes 512×128 of Cirrus optical coherence tomography (OCT) and volume scans of Spectralis OCT were reviewed in a consecutive series of patients presenting between December 2008 and March 2009 with vitreomacular adhesion in exudative AMD.

Results 30 eyes of 25 patients with exudative AMD and vitreomacular adhesion were studied. 50% had type III lesions, 46.7% occult and 3.3% predominantly classic lesions. The localisation of the adhesion corresponded in 100% with the area of the neovascularisation (CNV), in 73.3% traction directed towards the CNV and in 83.3% towards the optic disc could be noted. Spectral domain OCT and 3D visualisation enabled clearer localisation of vitreomacular adhesion and definition of resulting traction lines.

Conclusion There is a high prevalence of type III lesions within eyes with vitreomacular adhesions, and complete correspondence between the location of the adhesion and the CNV. There is also a high incidence of vitreopapillary adhesion in these cases, suggesting a possible role in pathogenesis.

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Genetics

Exp Eye Res. 2011 Jan 18. [Epub ahead of print]

Retinal pigment epithelial cells upregulate expression of complement factors after co-culture with activated T cells.

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Abstract

In this study we examined the effect of T cell-derived cytokines on retinal pigment epithelial (RPE) cells with respect to expression of complement components. We used an in vitro co-culture system in which CD3/CD28-activated human T cells were separated from the human RPE cell line (ARPE-19) by a membrane. Differential gene expression in the RPE cells of complement factor genes was identified using gene arrays,

and selected gene transcripts were validated by q-RT-PCR. Protein expression was determined by ELISA and immunoblotting. Co-culture with activated T cells increased RPE mRNA and/or protein expression of complement components C3, factors B, H, H-like 1, CD46, CD55, CD59, and clusterin, in a dose-dependent manner. Soluble factors derived from activated T cells are capable of increasing expression of complement components in RPE cells. This is important for the further understanding of inflammatory ocular diseases such as uveitis and age-related macular degeneration.

PMID: 21255569 [PubMed - as supplied by publisher]

Retina. 2011 Jan 26. [Epub ahead of print]

AUTOSOMAL RECESSIVE VITELLIFORM MACULAR DYSTROPHY IN A LARGE COHORT OF VITELLIFORM MACULAR DYSTROPHY PATIENTS.

Kinnick TR, Mullins RF, Dev S, Leys M, Mackey DA, Kay CN, Lam BL, Fishman GA, Traboulsi E, Iezzi R, Stone EM.

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PURPOSE: To report 11 cases of autosomal recessive vitelliform macular dystrophy and to compare their molecular findings and phenotypic characteristics with those of patients with the more common and well-described dominant form of the disease.

METHODS: Blood samples were obtained from 435 unrelated individuals with a clinical diagnosis of vitelliform macular dystrophy and screened for mutations in the coding sequences of BEST1. Medical records and retinal photographs of selected patients were reviewed.

RESULTS: Nine of the 435 probands were found to have 2 plausible disease-causing variations in BEST1, while 198 individuals were found to have heterozygous variations compatible with autosomal dominant inheritance. Inheritance phase was determined in three of the recessive families. Six novel disease-causing mutations were identified among these recessive patients: Arg47Cys, IVS7-2A>G, IVS7+4G>A, Ile205del12ATCCTGCTCCAGAG, Pro274Arg, and Ile366delCAGGTGTGGC. Forty-four novel disease-causing mutations were identified among the patients with presumed autosomal dominant disease. The phenotype of patients with recessive alleles for BEST1 ranged from typical vitelliform lesions to extensive extramacular deposits.

CONCLUSION: We provide evidence that two abnormal BEST1 alleles, neither of which causes macular disease alone, can act in concert to cause early-onset vitelliform macular dystrophy.

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J Biol Chem. 2011 Jan 26. [Epub ahead of print]

Disease-associated N-terminal complement factor H mutations perturb cofactor and decay-accelerating activities.

Pechtl IC, Kavanagh D, McIntosh N, Harris CL, Barlow PN.

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Abstract

Many mutations associated with atypical haemolytic uraemic syndrome (aHUS) lie within CCP modules 19-20 at the C terminus of the complement regulator factor H (FH). This region mediates preferential action of FH on self, as opposed to foreign, membranes and surfaces. Hence speculation on disease mechanisms focusses on deficiencies in regulation of complement activation on glomerular capillary beds. Here we investigate the consequences of aHUS-linked mutations (R53H and R78G) within the FH N-terminal CCP module that also carries the I62V variation linked to dense-deposit disease and age-related macular degeneration. This module contributes to a four-module C3b-binding site (FH1-4) needed for complement regulation and sufficient for fluid-phase regulatory activity. Recombinant FH1-4V62 and FH1-4I62 bind immobilized C3b with similar affinities (KD = 10-14 μM) while FH1-4I62 is slightly more effective than FH1-4V62 as cofactor for factor I-mediated cleavage of C3b. The mutant (R53H)FH1-4V62 binds to C3b with comparable affinity (KD ~12 μM), yet has decreased cofactor activities both in fluid phase and on surface-bound C3b, and exhibits only weak decay-accelerating activity for C3 convertase (C3bBb). The other mutant, (R78G)FH1-4V62, binds poorly to immobilised C3b (KD >35 μM), and is severely functionally compromised, having decreased cofactor and decay-accelerating activities. Our data support causal links between these mutations and disease; they imply that mutations affecting the N-terminal activities of FH, not just those in the C terminus, can predispose to aHUS. These observations reinforce the notion that deficiency in any one of several FH functional properties can contribute to the pathogenesis of this disease.

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Invest Ophthalmol Vis Sci. 2011 Jan 27. [Epub ahead of print]

Copy Number Variations in Candidate Genes in Neovascular Age-Related Macular Degeneration.

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Purpose: The pathogenesis of age-related macular degeneration (AMD) is strongly influenced by genetic factors, and single nucleotide polymorphisms have been consistently linked to AMD. Copy number variation (CNV), or variation in the number of copies of a particular segment of DNA, may also contribute to AMD pathogenesis. This study evaluated CNVs in candidate genes that have been reported to be linked to AMD.

Methods: Study participants included 131 persons with neovascular AMD and 103 elderly persons without AMD who were evaluated by retinal specialists at the National Eye Institute. DNA was collected from peripheral whole blood, and duplex RT-PCR based copy number (CN) assays were performed for the genes CCR3, CFH, CX3CR1, ERCC6, HTRA1, and VEGF. Quantitative CNs (CN=0, 1, 2, or 3+) were determined.

Results: Novel CNVs were discovered in CCR3, CX3CR1 and ERCC6. The unadjusted data suggested that CN=3+ for CX3CR1 might be mildly protective against AMD, but this trend did not persist after adjustment for age. AMD cases appeared to have an elevated mean CFH CN relative to controls (2.13, 95% CI: 2.05-2.21 vs. 2.01, 95% CI: 1.92-2.09 copies, p=0.05). No significant associations between CNV and AMD were observed for the remaining genes.

Conclusions: The methods described are suitable for quantitative characterization of CNV in candidate

genes. We identified CNVs in AMD-associated genes but did not find strong evidence for a link with neovascular AMD.

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Epidemiology and pathogenesis

Graefes Arch Clin Exp Ophthalmol. 2011 Jan 28. [Epub ahead of print]

Subfoveal choroidal thickness in typical age-related macular degeneration and polypoidal choroidal vasculopathy.

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PURPOSE: To investigate the subfoveal choroidal thickness in eyes with typical age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV), using enhanced depth imaging optical coherence tomography.

METHODS: Retrospective observational case series of 44 eyes of 44 patients (12 females and 32 males) with typical AMD or PCV located in the subfoveal region. Cross-sectional images of the choroid of each of the involved eyes were obtained by a spectral-domain OCT. The choroidal thickness under the fovea was retrospectively studied.

RESULTS: Of the 44 eyes involved in this study, 21 eyes were diagnosed as typical AMD and the other 23 eyes were diagnosed as PCV. The difference in subfoveal choroidal thickness between the eyes with typical AMD (245 μm) and those with PCV (293 μm) was statistically significant, even after adjusting for age, spherical equivalent, and gender distribution (P = 0.045). When compared to eyes with subfoveal choroidal thickness less than 300 μm, those with subfoveal choroidal thickness of 300 μm or more were 5.6 times more likely to have PCV (adjusted odds ratio 5.60, 95% confidence interval 1.30-24.0, P = 0.021).

CONCLUSIONS: The choroid under the fovea was thicker in eyes with PCV than those with typical AMD. This result suggests that the choroidal vascular lesion seen in PCV may not be just the choroidal neovascularization accompanied by saccular capillary dilations at the border, but may have a significant structural difference in the choroid compared to typical AMD.

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Invest Ophthalmol Vis Sci. 2011 Jan 27. [Epub ahead of print]

Mitochondrial DNA damage and repair in RPE associated with aging and age-related macular degeneration.

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Purpose: Mitochondrial DNA damage may be associated with age-related diseases, such as age-related macular degeneration (AMD). The present study was designed to test whether the frequency of mitochondrial DNA (mtDNA) damage, heteroplasmic mtDNA mutations, and repair capacity correlates with progression of AMD.

Methods: Macular and peripheral RPE cells were isolated and cultured from human donor eyes with and

without AMD history. The stages of AMD were graded according to the Minnesota Grading System. Confluent primary RPE cells were used to test the frequency of endogenous mtDNA damage by quantitative PCR. Surveyor(TM) mutation detection kits were used to detect heteroplasmic mtDNA mutation. To test the mtDNA repair capacity, cultured RPE cells were allowed to recover for 3 and 6 hours after exposure to H(2)O(2) and then repair assessed by quantitative PCR. The levels of human OGG1 protein, which is associated with mtDNA repair, were analyzed by Western Blot.

Results: Our study showed that mtDNA damage increased with aging, and more lesions occurred in RPE cells from the macular region relative to the periphery. Furthermore, mtDNA repair capacity decreased with aging, with less mtDNA repair capacity in the macular region compared with the periphery in samples from aged subjects. Most interestingly, the mtDNA damage is positively correlated with the grading level of AMD, while repair capacity is negatively correlated. In addition, more mitochondrial herteroplasmic mutations were detected in eyes with AMD.

Conclusion: Our data show macula-specific increases in mtDNA damage, heteroplasmic mutations and diminished repair that are associated with aging and AMD severity.

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