FEATURED ARTICLE

A multi-centre prospective evaluation of THEIA™ to detect diabetic retinopathy (DR) and diabetic macular oedema (DMO) in the New Zealand screening program.

Eye (London, England) 2022 Sep 3

Vaghefi E, Yang S, Xie L, Han D, Yap A, Schmeidel O, Marshall J, Squirrell D.

Purpose: To validate the potential application of THEIA™ as clinical decision making assistant in a national screening program.

Method: A total of 900 patients were recruited from either an urban large eye hospital, or a semi-rural optometrist led screening provider, as they were attending their appointment as part of New Zealand Diabetic Eye Screening Programme. The de-identified images were independently graded by three senior specialists, and final results were aggregated using New Zealand grading scheme, which was then converted to referable/non-referable and Healthy/mild/more than mild/sight threatening categories.

Results: THEIA™ managed to grade all images obtained during the study. Comparing the adjudicated images from the specialist grading team, "ground truth", with the grading by the AI platform in detecting "sight threatening" disease, at the patient level THEIA™ achieved 100% imageability, 100% [98.49-100.00%] sensitivity and [97.02-99.16%] specificity, and negative predictive value of 100%. In other words, THEIA™ did not miss any patients with "more than mild" or "sight threatening" disease. The level of agreement between the clinicians and the aggregated results was (k value: 0.9881, 0.9557, and 0.9175), and the level of agreement between THEIA™ and the aggregated labels was (k value: 0.9515). CONCLUSION: This multi-centre prospective trial showed that THEIA™ did not miss referable disease when screening for diabetic retinopathy and maculopathy. It also had a very high level of granularity in reporting the disease level. As THEIA™ has been tested on a variety of cameras, operating in a range of clinics (rural/urban, ophthalmologist-led\optometrist-led), we believe that it will be a suitable addition to a public diabetic screening program.

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BIOMARKERS

Relative ellipsoid zone reflectivity and its association with disease severity in age-related macular degeneration: a MACUSTAR study report.

Scientific Reports 2022 Sep 2

Saßmannshausen M, Behning C, Isselmann B, Schmid M, Finger RP, Holz FG, Schmitz-Valckenberg S, Pfau M; MACUSTAR Consortium, Thiele S.

Quantification of the relative ellipsoid zone reflectivity (rEZR) might be a structural surrogate parameter for an early disease progression in the context of age-related macular degeneration (AMD). Within the European multicenter, cross-sectional MACUSTAR study, we have devised an automatic approach to determine the mean rEZR [arbitrary units, AU] at two independent visits in SD-OCT volume scans in study participants. Linear mixed-effects models were applied to analyze the association of AMD stage and AMD associated high-risk features including presence of pigmentary

abnormalities, reticular pseudodrusen (RPD), volume of the retinal-pigment-epithelial-drusenoid-complex (RPEDC) with the rEZR. Intra-class correlation coefficients (ICC) were determined for rEZR reliability analysis. Within the overall study cohort (301 participants), we could observe decreased rEZR values (coefficient estimate ± standard error) of - 8.05 ± 2.44 AU (p = 0.0011) in the intermediate and of - 22.35 ± 3.28 AU (p < 0.0001) in the late AMD group. RPD presence was significantly associated with the rEZR in iAMD eyes (- 6.49 ± 3.14 AU; p = 0.0403), while there was a good ICC of 0.846 (95% confidence interval: 0.809; 0.876) in the overall study cohort. This study showed an association of rEZR with increasing disease severity and the presence of iAMD high-risk features. Further studies are necessary to evaluate the rEZR's value as a novel biomarker for AMD and disease progression.

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PATHOPHSIOLOGY

Retinal microvasculature and choriocapillaris impairments according to the stage of dry age-related macular degeneration.

Clinical & experimental ophthalmology 2022 Sep 6

Kim JT, Jun JH, Lee SC, Lee MW.

Background: We aimed to analyse the retinal microvasculature and choriocapillaris according to the dry age-related macular degeneration (AMD) stage and to identify factors associated with their microvasculatures.

Methods: Patients were divided into four groups: normal controls; early; intermediate; and advanced AMD groups. The vessel density (VD) of superficial capillary plexus (SCP), deep capillary plexus (DCP), and choriocapillaris was compared using optical coherence tomography angiography among the groups. Linear regression analysis was performed to identify factors associated with the VD.

Results: The VDs of the SCP were 22.1 ± 5.7, 19.1 ± 5.4, 18.0 ± 6.4, and 12.2 ± 6.4% (P < 0.001); the VDs of the DCP were 22.4 ± 4.5, 20.7 ± 4.3, 18.1 ± 5.3, and 14.6 ± 5.8% (P < 0.001); the VDs of the choriocapillaris were 29.4 ± 3.7, 26.4 ± 4.8, 24.5 ± 4.9, and 24.2 ± 3.7% (P < 0.001) in the control, early, intermediate, and advanced groups, respectively. AMD stage and age were significantly associated with the VDs of all layers, and the VDs of the SCP and DCP were associated with visual acuity (both P < 0.001). Additionally, hypertension was associated with the VDs of the DCP (P = 0.027) and choriocapillaris (P = 0.024).

Conclusions: The retinal microvasculature and choriocapillaris tended to become more impaired as the AMD stage progressed. Age was significantly associated with the microvasculature impairments of all layers, and hypertension was significantly associated with impairments of the DCP microvasculature and choriocapillaris.

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GENETICS

An assessment of prevalence of Type 1 CFI rare variants in European AMD, and why lack of broader genetic data hinders development of new treatments and healthcare access.

PLoS One 2022 Sep 6

Jones AV, Curtiss D, Harris C, Southerington T, Hautalahti M, Wihuri P, Mäkelä J, Kallionpää RE, Makkonen E, Knopp T, Mannermaa A, Mäkinen E, Moilanen AM, Tezel TH; SCOPE Study group, Waheed NK.

Purpose: Advanced age-related macular degeneration (AAMD) risk is associated with rare complement Factor I (FI) genetic variants associated with low FI protein levels (termed 'Type 1'), but it is unclear how variant prevalences differ between AMD patients from different ethnicities.

Methods: Collective prevalence of Type 1 CFI rare variant genotypes were examined in four European AAMD datasets. Collective minor allele frequencies (MAFs) were sourced from the natural history study SCOPE, the UK Biobank, the International AMD Genomics Consortium (IAMDGC), and the Finnish Biobank Cooperative (FINBB), and compared to paired control MAFs or background population prevalence rates from the Genome Aggregation Database (gnomAD). Due to a lack of available genetic data in non-European AAMD, power calculations were undertaken to estimate the AAMD population sizes required to identify statistically significant association between Type 1 CFI rare variants and disease risk in different ethnicities, using gnomAD populations as controls.

Results: Type 1 CFI rare variants were enriched in all European AAMD cohorts, with odds ratios (ORs) ranging between 3.1 and 7.8, and a greater enrichment was observed in dry AMD from FINBB (OR 8.9, 95% CI 1.49-53.31). The lack of available non-European AAMD datasets prevented us exploring this relationship more globally, however a statistical association may be detectable by future sequencing studies that sample approximately 2,000 AAMD individuals from Ashkenazi Jewish and Latino/Admixed American ethnicities.

Conclusions: The relationship between Type 1 CFI rare variants increasing odds of AAMD are well established in Europeans, however the lack of broader genetic data in AAMD has adverse implications for clinical development and future commercialisation strategies of targeted FI therapies in AAMD. These findings emphasise the importance of generating more diverse genetic data in AAMD to improve equity of access to new treatments and address the bias in health care.

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Common and rare genetic risk variants in age-related macular degeneration and genetic risk score in the Coimbra eye study.

Acto Opthalamologica 2022 Aug 29

Farinha C, Barreto P, Coimbra R, Cachulo ML, Melo JB(5), Cunha-Vaz J, Lechanteur Y, Hoyng CB, Silva R.

Purpose: To determine the contribution of common and rare genetic variants in age-related macular degeneration (AMD) in a Portuguese population from the Coimbra Eye Study (CES), and the genetic risk score (GRS).

Methods: Participants underwent ophthalmologic examination and imaging. A centralized reading centre performed AMD staging. Genetic sequencing was carried out with the EYE-RISK assay. Sixty-

nine single nucleotide polymorphisms (SNPs) were genotyped and tested for association with AMD. Case-control and progression-to-AMD analyses were performed using logistic regression to assess allelic odds ratio (OR) at a 95% confidence interval (CI) for each variant. GRS was calculated for cases/controls and progressors/non-progressors. Cumulative impact of rare variants was compared between cases/controls using logistic regression.

Results: In case-control analysis (237 cases/640 controls) variants associated with risk of disease were: ARMS2 rs10490924, ARMS2_HTRA1 rs3750846, CFH rs35292876, SLC16A8 rs8135665, TGFBR1 rs1626340. Major risk variants ARMS2/HTRA1 rs3750846, CFH rs570618 and C3 rs2230199 had unexpected lower allele frequency (AF), and the highest risk-conferring variant was a rare variant, CFH rs35292876 (OR, 2.668; p-value = 0.021). In progression-to-AMD analysis (137 progressors/630 non-progressors), variants associated with risk of progression were ARMS2 rs10490924, ARMS2_HTRA1 rs3750846, CFH rs35292876. GRS of cases/controls was 1.124 ± 1.187 and 0.645 ± 1.124 (p-value < 0.001), and of progressors/non-progressors was 1.190 ± 1.178 and 0.669 ± 1.141 (p-value < 0.001). Higher proportion of pathogenic rare CFH variants was observed in cases (OR, 9.661; p-value < 0.001). CONCLUSIONS: Both common and rare variants were associated with AMD, but a CFH rare variant conferred the highest risk of disease while three major risk variants had a lower-than-expected AF in our population originary from a geographic region with lower prevalence of AMD. GRS was still significantly higher in AMD patients. Damaging CFH rare variants were cumulatively more common in AMD cases.

DOI: 10.1111/aos.15232

CASE REPORTS

Bilateral Cystoid Macular Edema after COVID-19: 1 Year Follow Up.

Ocular Immunology and Inflammation 2022 Sep 8

Kılıçarslan O, Yılmaz Çebi A, Uçar D, Şentürk F, Aras C.

Purpose: The aim is to report a case of bilateral macular edema after COVID-19 pneumonia.

Case report: A 66-year-old male patient with history of COVID-19 pneumonia presented to us with decreased vision. Examination showed bilateral cystoid macular edema (CME), which was confirmed on optical coherence tomography (OCT). There were no findings in the fundus examination. He had no systemic disease, drug or surgery history, or any factors that could explain the clinic presentation. Work-up for uveitis was unremarkable. After topical therapy with brinzolamide 1% and nepafenac 0.1%, macular edema regressed in a month.

Conclusion: This is an unusual case of CME in previous COVID-19 infection. This presentation may be a parainfectious or a post-viral manifestation of COVID-19.

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Solar maculopathy secondary to sunlight exposure reflected from the screen of mobile devices: two case reports.

Journal of medical case reports 2022 Sep 6

Marticorena J, Honrubia A, Ascaso J.

Background: Solar maculopathy is a well described clinical entity that usually occurs in patients that have gazed directly the sun. In this report we describe the first two cases of solar maculopathy in individuals exposed to sunlight reflected from the screen of mobile devices in the absence of direct sun gaze.

Cases description: Case 1. A 30-year-old Caucasic man presented with bilateral metamorphopsia, central scotoma and decreased visual acuity two days after being reading for four hours with his tablet computer in a terrace of a ski center. CASE 2: A 20-year-old Caucasic woman was examined for bilateral decrease of visual acuity and central scotoma after being at the beach the day before and reading with her mobile phone for 3 hours. Both patients denied gazing directly to sunlight at any moment. In each case, exploration revealed fundus and OCT images compatible with the typical features of solar maculopathy. After 2 years of follow-up, in absence of any specific treatment, Case 1 had a complete resolution of the fundus alterations, while Case 2 still presented defects of the outer retinal layers. In both cases, an exposure to sunlight reflected from the screen of their mobile devices was documented in environments where solar radiation is thought to be augmented.

Conclusion: Sunlight reflection from a display screen needs to be considered as a possible risk factor for increased solar radiation and a subsequent risk of solar maculopathy.

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Sub-retinal pigment epithelium tubules in non-neovascular age-related macular degeneration.

Scientific Reports 2022 Sep 7

Fragiotta S, Parravano M, Sacconi R, Costanzo E, De Geronimo D, Prascina F, Capuano V, Souied EH, Han IC, Mullins R, Querques G.

To describe a novel optical coherence tomography (OCT) signature resembling sub-retinal pigment epithelium (RPE) tubules (SRT) in non-neovascular age-related macular degeneration (AMD). Patients suffering from non-neovascular AMD with complete medical records and multimodal imaging were retrospectively revised in three different tertiary care centers. Multimodal imaging included color fundus photograph, spectral-domain OCT (Spectralis, Heidelberg Engineering, Germany), fundus autofluorescence, OCT angiography (RTVue XR Avanti, Optovue, Inc., Fremont, CA). A total of 7 eyes of 7 patients with drusenoid pigment epithelium detachment (PED) were consecutively analyzed. The sub-RPE tubules appeared as ovoidal structures with a hyperreflective contour and hyporeflective interior appreciable in the sub-RPE-basal lamina (BL) space on OCT B-scan. The anatomical location of the sub-RPE formations was lying above the Bruch's membrane in 5/7 cases (71.4%) or floating in the sub-RPE-BL space in 2/7 cases (28.6%). En-face OCTA revealed a curvilinear tubulation-like structure corresponding to SRT without flow signal. Sub-RPE tubules represent a newly identified OCT signature observed in eyes with drusenoid PED. The presumed origin may include a variant of calcified structure or alternatively activated RPE cells with some residual BL or basal laminar deposits attracted to BrM for craving oxygen.

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REVIEWS

Long-term outcomes for patients treated for macular oedema secondary to retinal vein occlusion: a systematic review.

BMJ Open Ophthalmology 2022 Jun 7

Hunter A, Williams M.

This systematic review assessed the long-term outcomes for patients treated with intravitreal antivascular endothelial growth factor or dexamethasone for macular oedema (MO) secondary to retinal vein occlusion (RVO). Studies investigating patients of all ages with MO due to RVO only were included. The review was deliberately broad in scope, including comparative and non-comparative studies to ensure inclusion of real-world type evidence. Risk of bias was assessed. In total, 76 data sets were included (10 775 participants). Overall, mean best-corrected visual acuity (BCVA) improved from baseline to 5 years by 16.1 letters ($p<0.01$). BCVA improved from baseline in both central RVO (CRVO) and branch RVO (BRVOs) at 2 years, by 9.1 ($p<0.01$) (difference from baseline in CRVOs) and 9.1 ($p<0.01$) letters, respectively. At 5 years, BCVA improved from baseline in CRVOs by 15.6 letters and in BRVOs by 16.2; the difference between RVO types was not significant ($p=0.18$). Two studies had 5-year data for ranibizumab, and improvement was evident. There was no significant difference between outcomes in randomised controlled trials (RCTs) compared with non RCTs. These results suggest a benefit to receiving long-term intravitreal treatments for MO due to RVO.

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