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ARTICLE

Prevalence of optic disc haemorrhages in an elderly UK Caucasian population and possible association with reticular pseudodrusen—the Bridlington Eye Assessment Project (BEAP): a cross-sectional study (2002–2006)

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Abstract

Aims To determine disc haemorrhage (DH) prevalence in an elderly UK population—the Bridlington Eye Assessment Project (BEAP).

Methods Thirty-degree fundus photographs (3549 participants ≥65 years) were graded for DH/macula changes. Glaucoma evaluation included Goldmann tonometry, 26-point suprathreshold visual-fields and mydriatic slit-lamp assessment for glaucomatous optic neuropathy.

Results In all, 3548 participants with photographs in at least one eye. DHs were present in 53 subjects (1.49%), increasing from 1.17% (65- to 69-year age group) to 2.19% (80- to 84-year age group), $p = 0.06$. DH was found in 9/96 (9.38%) right eyes (RE) with open-angle glaucoma (OAG). Two of twelve RE (16.67%) with normal-tension glaucoma (NTG) had DH. Prevalence in eyes without glaucoma was lower (32/3452, [0.93%]). Reticular pseudodrusen (RPD) occurred in 170/3212 (5.29%) subjects without DH, and 8/131 subjects (6.11%) with OAG. Twenty eyes had NTG, two of whom had RPD (10%) ($p = 0.264$). Within a logistic regression model, DH was associated with glaucoma (OR 10.2, 95% CI 5.32–19.72) and increasing age (OR 1.05, 95% CI 1.00–1.10, $p = 0.03$). DH was associated with RPD ($p = 0.05$) with univariate analysis but this was not statistically significant in the final adjusted model. There was no significant association with gender, diabetes mellitus (DM), hypertension treatment or Age-related Macular Degeneration (AMD) grade.

Conclusion DH prevalence is 1.5% in those over 65 years old and significantly associated with glaucoma and increasing age. There appears to be increased RPD prevalence in eyes with DH and NTG with age acting as a confounding factor. Larger studies are required to fully assess the relationship and investigate a possible shared aetiology of choroidal ischaemia.

Introduction

Optic disc haemorrhages (DHs) in association with glaucoma are characteristically flame or splinter shaped, occurring at the border of, or involving the optic nerve head. Originally reported by Bjerrum [1], the term 'glaucoma haemorrhagicum' was used to describe patients with glaucoma and DH. They are considered a hallmark for glaucomatous optic neuropathy [2–9]. Approximately 100 years later, Drance and Begg [10] recognised the association between DH and glaucoma progression after noting a patient with 'chronic simple glaucoma' and asymptomatic DH developed a new corresponding visual field (VF) defect with subsequent neuroretinal rim focal thinning. Drance et al. [2] later published their finding that 71% of primary

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open-angle glaucoma (POAG) patients with evidence of DH developed progressive VF defects, compared to 33% of those without. They reported that among patients with ocular hypertension, 34% with a visible DH developed VF defects, compared to 3% of those without [2].

Several population-based studies have published the prevalence of DHs, demonstrating they are infrequently found in normal eyes (0.9–3.4%) [4, 11–15]. They have their highest prevalence (11–46%) in eyes with normal-tension glaucoma (NTG) [13, 16–18], with lower prevalence among eyes with POAG (2–37%) and OHT (0.4–10%) [13, 14, 17]. There are reports DHs are more common in women, with increasing age and vascular disease [13]. Other associations include diabetes mellitus (DM) [13, 19], migraine [13], pseudoexfoliation [13], aspirin use [19] and systemic hypertension [13, 20]. Jonas et al. reported disc morphology associations. Among POAG patients, those with small neuroretinal rims and large peripapillary beta zone changes were more likely to develop DH [21]. Hospital-based prevalence studies however have the disadvantage of selection bias. In the United Kingdom no population-based study has measured DH prevalence.

The purpose of the present study is to report DH prevalence in an elderly UK population, among those with and without glaucoma and investigate associations with systemic and ocular parameters.

Methods

Study design

The Bridlington Eye Assessment Project (BEAP) study methodology, including image acquisition and analysis is described elsewhere [22]. Briefly, the BEAP is a single-centre population-based prevalence study, designed to investigate the utility of screening for eye disease in an elderly population ≥65 years, using clinical examination by optometrists and digital imaging technology. Primary ophthalmic diseases studied were AMD, cataract and glaucoma. Bridlington is a coastal town in Yorkshire, UK, with a stable, predominantly Caucasian population. The study received approval from the local ethics committee (Scarborough and North East Yorkshire Local Ethics Research Committee; Ref No. PB/RH/02/288). Its methodology adhered to the tenets of the Declaration of Helsinki. Study recruitment occurred between 5 November 2002 and 29 March 2006. All participants were interviewed, in person, by a trained research nurse using a structured questionnaire, and examined by one of four specially trained optometrists with a pro-forma completed by research staff. Non-stereoscopic mydriatic fundus photography was performed with a Topcon fundus camera (model TRC NW6S) and Nikon 10-megapixel camera. Each eye had a 30° colour fundus photograph (CFP) taken, centred on the macula. In total, 3549 individuals attended the initial study examination (56% of the eligible population). Basic demographic information was available for all subjects within the sampling frame. Gender balance was similar for both attenders and non-attenders.

Two ophthalmologists (CW and RN) independently examined each photograph for the presence of DH. All CFPs were separately graded for other ocular pathologies, including AMD and reticular pseudodrusen (RPD) by one examiner (CW) using definitions and grids as described in the International Classification System for AMD and as reported elsewhere [22].

Grading was masked, in the absence of all demographic data, and results of ocular examinations, tests or final diagnoses. Each eye was graded separately. The final grade assigned to each participant was that of either eye.

DHs were defined as haemorrhages lying completely inside the optic nerve head, those extending beyond or those touching the optic disc border. Examples are shown in Figs. 1 and 2. Haemorrhages located completely outside the optic disc head were excluded, as they may be secondary to other ocular diseases. Eyes with visible diabetic retinopathy, retinal vein occlusions or collateral disc vessels and optic disc oedema, or eyes with signs of other ocular pathology, such as peripapillary choroidal neovascular membranes, were excluded from analysis. In eyes with DH the number, locations and shapes were recorded.

All photographs showing DH were reviewed by a glaucoma subspecialist (SAV) who acted as final arbiter.

Within the BEAP all subjects were assessed for glaucoma. Intraocular pressure (IOP) was measured using a

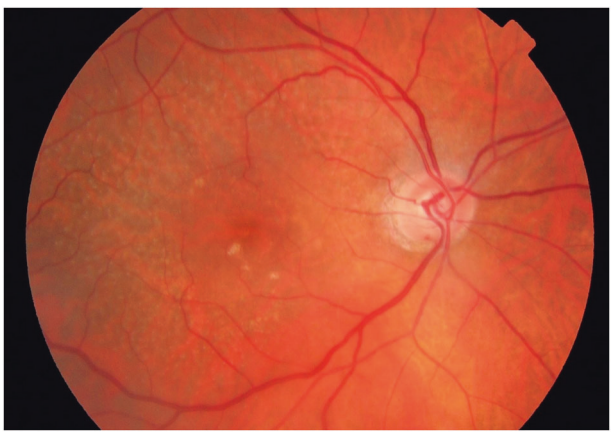

Fig. 1 Colour fundus photograph of right eye showing extensive dot and ribbon RPD. There is an inferior DH with associated thinning of the neuroretinal rim and a focal notch. There is temporal bayoneting at the optic disc edge. There is a tessellated appearance to the fundus with decreased pigmentation inferior to the optic disc and peripapillary pigmentary changes. There are sparsely visible choroidal vessels between the optic disc and macula

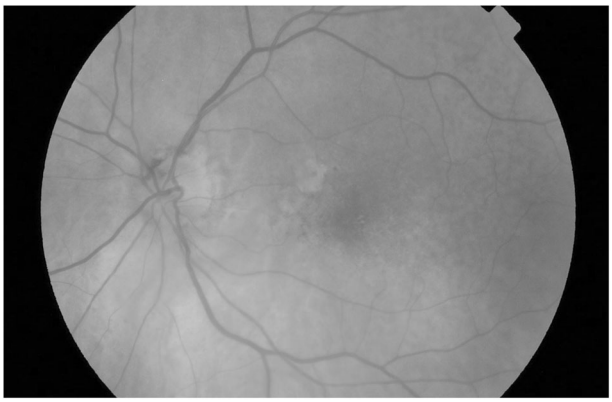

Fig. 2 Superonasal neuroretinal rim DH associated with co-morbid geographic atrophy and temporal ribbon RPD. There are some photographic features of age-related choroidal atrophy, including peripapillary atrophy and pigmentary changes. There is a large area of inferior scleral show

calibrated Goldmann applanation tonometer. VF testing using a Henson Pro 5000 automated perimeter, software v3.1.4 (Tinsley Instruments, Croydon, UK) with single-stimulus, suprathreshold, central 26-point strategy was employed. The test was automatically extended to 68 points if defects were detected. The perimeter automatically graded outputs as normal, suspect or defect. For study purposes, any defect including those classified as suspicious were treated as abnormal. Estimation of vertical cup to disc ratio was performed using a 90 D condensing lens by the examining optometrist, who recorded the presence of pathological features, including DH, bayonetting and focal notching, before deciding if the disc appeared abnormal using criteria developed by Jonas et al. [23, 24]. Subjects with abnormal VFs, raised IOP (≥21 mm Hg) or disc features suspicious for glaucoma were referred to the hospital eye service for assessment by one of four consultant ophthalmologists. A definitive clinical diagnosis of glaucoma would be assigned following clinic assessment or appropriate follow-up. All glaucoma diagnoses were reviewed by a single glaucoma subspecialist (SAV) using a minimum of 5 years longtitudinal data to confirm incident disease at referral.

Statistical methods

All data were analysed with Stata v14 (Stata Corp, College Station, Tx, USA). Associations between groups were explored using unpaired *t*-tests for continuous variables and chi-squared test for discrete variables. Where necessary, results were stratified using Mantal Haenzel methods. Logistic regression was used for multivariate analysis and to determine odd ratios in the final adjusted model and was computed using a stepwise approach with each relevant additional variable added sequentially and the model rechecked for change.

Results

In total, 3548 Caucasian participants had gradable photographs of the optic nerve in at least one eye, with 3255 having gradable CFP in both. DHs were present in 53 subjects (1.49% prevalence for either eye), in the ≥65-year age group. A total of 25 subjects with DH were female (47.2%). Males had a higher gender-specific prevalence (1.79% vs 1.26%) ($p = 0.19$); on multivariate logistical regression analysis this difference was not statistically significant (odds ratio (OR) female gender 0.65, confidence interval (CI) 0.37–1.14). DH frequency for right ($n = 41$, 77.4%) and left eyes ($n = 12$, 22.6%) appeared to be different. Mean age for subjects with DH was 77.01 years (SD 7.55 [Table 1]) and DH prevalence demonstrated a trend to increase with age from 1.17% in the 65- to 69-year age group, to a maximum of 2.19% in the 80- to 84-year age group ($p = 0.06$).

For right eyes, 32 out of 41 (78.0%) DHs occurred in eyes without a definite diagnosis of OAG.

In total, 96 of 3548 right eyes (2.7%) had open-angle glaucoma (OAG). Of all 41 right eyes with DH, 9 had definite OAG (22%), representing 9 out of 96 (9.38%) DH right eyes with definite OAG. Twelve right eyes were identified with NTG, of which 2 had DH (16.67%). The prevalence of DH in non-glaucomatous eyes was 0.93% (32 of 3452 eyes). In a univariate analysis, presence of DH was significantly ($p < 0.05$) associated with older age and NTG.

RPD occurred in 170 of 3212 (5.29%) subjects with no DH, and in 8 of 131 subjects (6.11%) with OAG. Twenty eyes had NTG, 2 of which had RPD (10%) ($p = 0.264$). In univariate analysis, DHs were significantly associated with the presence of RPD ($p = 0.048$). Among the 3264 subjects with gradable images (for both RPD and DH), 6 of 52 eyes (11.54%) with DH had RPD. Five of 53 eyes (9.43%) with DH had either geographic atrophy or neovascular AMD in their worse eye.

Within a logistic regression model, we found that DH was associated with glaucoma (OR 10.2, 95% CI 5.32–19.72) and increasing age (OR 1.05, 95% CI 1.00–1.10, $p = 0.03$) corresponding to annual 5% increase in risk. DH was associated with RPD ($p = 0.05$) in the univariate analysis but this was not significant in the final adjusted model. There was a weak association between RPD and DH ($p = 0.05$), which was not significant when we corrected for age (OR 1.87, CI 0.74–4.74, $p = 0.18$). There was no significant association between DH and gender, DM, hypertension treatment or AMD grade.

Table 1 The characteristics of patients with and without disc haemorrhages (DHs)

Variable	With DH	Without DH	Total	*p*-Value
Mean age [years] (95% confidence interval)	77.01 (74.93–79.09)	75.04 (74.84–75.23)	75.07 (74.87–75.26)	0.016[a]
Gender				
Male	28 (1.80)	1530 (98.20)	1558	0.195[b]
Female	25 (1.26)	1953 (98.74)	1978	
Diabetes mellitus				
Yes	3 (0.85)	352 (99.15)	355	0.283[b]
No	50 (1.58)	3121 (98.42)	3171	
Hypertension treatment				
Yes	27 (1.60)	1662 (98.40)	1689	0.701[b]
No	26 (1.44)	1780 (98.56)	1806	
Patients with no AMD in worse eye (Rotterdam grade 0)				
Yes (grade 0)	20 (1.5)	1317 (98.50)	1337	0.991[b]
No (grade 1–4)	33 (1.50)	2166 (98.50)	2199	

Data are: number (percentage) unless otherwise stated

[a]*t*-test

[b]Chi^2

Discussion

Despite their importance and association with glaucoma, no UK population-based report of DH prevalence exists, with a paucity of studies from European Caucasian populations. Many reports are hospital-based focusing on subjects with an established glaucoma diagnosis, ocular hypertension or documented DH, with associated selection bias [3, 4, 13, 25, 26]. The prevalence of DH in the Bridlington (UK) population (aged >65 years) of 1.5% is comparable to that in other large population-based studies, including 1.2% in Japan [14], Australia (1.4%) [13], United States (0.9%) [11] and China (1.2%) [12]. To date our finding represents the highest population-based prevalence, which may reflect the older age of our cohort.

In this study, DH was significantly associated with age, with prevalence reaching 2.19% in the 80- to 84-year age group. This is consistent with previous population [12] and hospital-based studies [21, 27]. Jonas et al. reported an OR of 1.48 for 10-year increase in age for DH development [21]. In the Ocular Hypertension Treatment Study, patients with DH were older than those without (59.0 vs 55.2 years, $p < 0.01$) [27]. Our finding of a 1.05 increased risk of DH per year is similar to that in the Korean National Health and Nutritional Examination Survey (1.04-fold increased risk per year) [28].

Previous studies have reported conflicting results relating to the association between DH and gender. In this study, DH prevalence was higher in men but the difference was not statistically significant (OR female gender 0.65, CI 0.37–1.14). This is in line with population-based studies from South Korea [29] and China [12]. In the Blue Mountains Eye Study (BMES), DH prevalence was higher in woman (OR 1.9, CI 1.0–3.5) [13], after adjustment for age and glaucoma, while a female preponderance has also been reported elsewhere [11, 30, 31].

This study confirms most DH occur in healthy individuals with no (current) diagnosis of glaucoma, while only 27% of DH occur in glaucomatous eyes (OAG or NTG), reflecting the relative rarity of OAG. This finding is higher than in the Beijing Eye Study (where 20% of DH was detected in glaucomatous eyes) [12].

Glaucoma remains the most important disease associated with DH and the reported prevalence among glaucoma patients varies considerably, ranging from 4.2 to 17.6% for POAG and 19.4 to 35.3% for NTG [13, 16, 32–34]. In our study DH prevalence in subjects with OAG was 9.4%, being similar to other population-based reports, including 13.8% in the BMES, 8.8% in the Beijing Eye Study and 8.2% in the Tajimi study [31]. Our findings of higher DH prevalence among eyes with NTG (16.7%) is in keeping with previously published reports [13].

The positive predictive value (PPV) of DH varies throughout the literature, appearing to reflect the type of glaucoma most prevalent within the population. In a Japanese study, where NTG is most prevalent, the PPV was high (52.9%) [14]. Of clinical relevance is the finding that a DH in our UK population has a PPV of 27% for OAG or NTG, as 27% of right eye DHs was found in eyes with OAG or NTG. This is similar to findings from other studies within predominantly Caucasian populations of European ancestry [13].

The putative finding of higher DH frequency for right eyes ($n = 41$, 77.4% vs $n = 12$, 22.6%) was unexpected, likely reflecting a chance finding. Laterality of DH is often

not reported or discussed. The unit of study is often either eye. In the BMES [13], DH prevalence was highest for left eyes (34/56, 60.7% vs 22/56, 39.3%). Siegner et al. [8] in a hospital-based population reported DHs were identified in 51% of right eyes. It has been demonstrated that low diastolic perfusion pressure is an independent risk factor for development of OAG [35], with suggestions that lower ocular perfusion pressure results in reduced ocular blood supply, resulting in glaucomatous optic neuropathy. Differences in systolic BP between arms can predict increased risk of cardiovascular events and all-cause mortality over a 10-year period in people with hypertension [36]. Some studies have suggested that diastolic BP is, on average, lower in the right arm and may be related to differing pulse pressures along the aorta [36–38]. However, the literature is inconsistent and inconclusive.

The pathogenesis of DH has not been fully elucidated. We report a newly described ocular association between DH and RPD, which may offer further insight into DH aetiology. We draw comparisons between demographic and pathological similarities among subjects with RPD, DH and NTG, and propose they may share an aetiological connection through choroidal ischaemia.

Within the BEAP, RPD are more common than recognised in prior population-based studies, with a prevalence of 5% in persons aged >65 years. Like NTG, RPD are consistently more prevalent in females. Their prevalence, like NTG, increases significantly with age, reaching a maximum of 27% in persons aged >90 years [22]. In the current study RPD prevalence is increased in individuals with NTG (11.5%) when compared to the population as a whole (5%), or when compared to all subjects with OAG (6.11%); in a univariate model, DHs were associated with RPD ($p = 0.048$), although this association was lost in multivariate analysis. Given the relative rarity of DH and RPD, and small numbers involved (with age acting as a confounding factor), a larger sample size may be required to confirm or refute any genuine association.

Arnold et al. [39] speculated that RPD result from poor choroidal perfusion after describing fibrosis within choroidal stroma between large choroidal veins. While choroidal thinning is consistently found in eyes with RPD [40, 41], juxtapapillary choroidal thinning has been documented in eyes with NTG [42–44]. Others have demonstrated reduced blood flow in the peripapillary retina in NTG eyes [45, 46], suggesting blood flow deficits may accompany or contribute to NTG. RPD may form part of a spectrum of chorioretinal changes seen in age-related choroidal atrophy, in which peripapillary atrophy (PPA), tessellation of the fundus, choroidal thinning and glaucoma are described associations [47]. There is increasing evidence of an association between RPD and cardiovascular disease and risk factors, including hypertension [48] and angina [49]. A recent publication demonstrated an association with diffuse-trickling Geographic Atrophy (GA) (which is strongly associated with RPD) and cardiovascular disease, particularly in males [50], and in the <65-year age group, 54% of patients had previously been admitted to hospital with cardiovascular disease, including hypertensive crisis, angina and myocardial infarction [50]. Similar associations between vascular insufficiency and NTG have been raised. Migraines are associated with transient vasospastic episodes that can result in impaired cerebral blood flow and have been consistently associated with NTG [51, 52] and progression of NTG [53]. In the Low-Pressure Glaucoma Treatment Study a history of migraine, low systolic blood pressure and use of systemic β blockers were associated with DH [54]. Hypertension, like RPD, has also been associated with DH in NTG [20].

PPA is another known feature shared among subjects with NTG (often with cupping most pronounced in areas of RPE loss) [55], DH [56] and RPD [57], offering further biological plausibility into a shared common pathway. Interestingly, flame-shaped DH occur most frequently in a superotemporal location [13]. Similarly, RPD have increased prevalence within the superotemporal macula [58]. We hypothesise that RPD, DH and NTG, in some instances, may be manifestations of the same aetiological pathway of choroidal ischaemia. We highlight the short posterior ciliary arteries (SPCA) supply both the choroid and prelaminar portion of the optic nerve head, along with the peripapillary choroid. We hypothesise chronic ischaemia via the SPCA may result in a spectrum of overlapping changes including DH, PPA, RPD and NTG in some individuals. Large prospective studies in NTG patients are required to investigate this association further. Utilisation of multimodal imaging for the optic disc, peripapillary area and macula choroid, with perfusion studies would be invaluable.

The possible association of RPD and NTG is important. The Beaver Dam Eye Study reported not only an association between RPD and glaucoma, but the highest 15-year incidence of AMD among subjects with RPD (43% and 46% in right and left eyes, respectively) [58]. This was twice the risk when compared to subjects with soft indistinct drusen. If RPD, DH and NTG are associated through shared aetiological mechanisms, patients with NTG will need appropriate macula imaging in clinics, advice regarding risk of AMD with provision of lifestyle advice and amsler grid for home screening. Similarly, clinicians should have a high index of suspicion while reviewing patients with RPD, paying attention to optic disc morphology for features of NTG, being aware of potential difficulties in diagnosing NTG in patients with AMD. Moreover, there is evidence suggesting patients with AMD and glaucoma pose extra hazards such as increased difficulties walking safely when compared to patients with glaucoma alone [59]. This

is not surprising when glaucoma predominantly affects tasks requiring contrast discrimination and peripheral vision/light-dark adaptation [60], while AMD influences tasks involving central vision such as reading and recognising faces [61].

Limitations of this study include its purely Caucasian participants, which could limit generalisability to the wider UK population. Optic disc and macula imaging was limited to non-stereoscopic CFPs. Multimodal imaging would have been preferred for both, particularly for detecting RPD. Prospective follow-up would have been preferred. While we have corrected for the majority of important co-variants, there are known associations that were not specifically questioned such as a history of Raynaud's phenomenon, migraines and use of β blockers or anticoagulants.

Summary

What was known before

- DHs are an infrequent finding in normal eyes but are common in eyes with NTG.
- DHs are associated with increasing age, vascular disease and female gender.

What this study adds

- This is the first UK population-based study to report prevalence of DH.
- This is the first study to report a possible increased prevalence of RPD in eyes with DH and NTG, suggesting a possible shared aetiology of choroidal ischaemia, but further larger studies are required to confirm these findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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