Phenotypic Subtypes of Glaucoma Patients with Small & Large Optic Discs

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Background

- Glaucoma, the second leading cause of blindness worldwide, is a heterogeneous family of eye disorders that share a final common pathway of progressive optic nerve degeneration [1,2]
- Multifactorial pathogenetic factors are at play in different glaucomatous individuals but are poorly understood, and current therapeutic strategies are not curative [1,2]
- Due to glaucoma's insidious and irreversible nature, early detection and treatment prior to severe progression are essential to vision preservation and improved prognoses [1,2]
- However, optic disc size varies substantially in the population and can make glaucoma more difficult to manage and progression more difficult to predict [3]
- Most optic nerve grading systems and AI algorithms do not accurately account for or parse through discs that lie outside the average range, leading to gaps in the scientific literature

Objectives

1. Conduct a comprehensive subgroup analysis of covariates against the rate of visual field (VF) decay among glaucoma patients with small and large optic discs
2. Identify and describe clinically discernible phenotypic subtypes of glaucoma among these patients

Methods

1. **Study population:** Patients with glaucoma in the UCLA Stein Eye Institute Glaucoma Division, N = 4,505
   - Disc measurements based on Spectralis OCT, Cirrus OCT, and/or HRT values
   - Small disc criteria: ≤5th percentile, ≤1.3 mm^2, N = 219
   - Large disc criteria: ≥95th percentile, ≥2.9 mm^2, N = 165
2. **Clinical covariates of interest:** Demographics, systemic comorbidities, glaucoma history, ocular comorbidities, ocular measurements, and visual fields
3. **Outcomes:** Rate of glaucomatous visual field (VF) deterioration based on the Glaucoma Rate Index (GRI), which estimates the rate of change on a normalized scale to categorize worsening eyes into fast vs. slow progressors
4. **Statistical analysis:** Logistic regression models in large and small disc populations, including all clinical covariates as predictors and GRI < -3 as outcome
5. **Disc photo analysis:** Glaucoma specialist (V.L.T) review of optic disc photos from the 10 highest and lowest GRI scores among small and large disc populations
6. **Qualitative review:** Combined review of statistical and disc photo analyses to identify phenotypic subclasses of small and large discs at high and low risks of glaucomatous progression

Results

Table 1. **Optic Disc Morphology Patterns in Glaucomatous Eyes with Non-Progressive vs. Progressive GRI (VF) Deterioration**

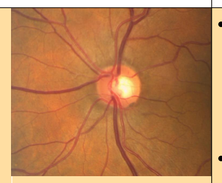
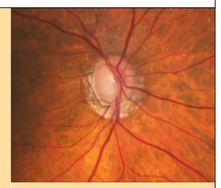
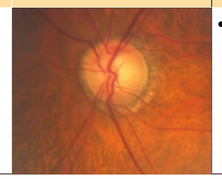
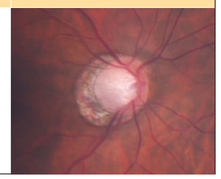
Disc Size	Non-Progressors		Progressors	
Small	• Round shape with full neuroretinal rim (NRR) and no peripapillary atrophy (PPA)		• Temporal tilt with heavy focal PPA with possible focal thinning • Round shape with light 360 PPA and diffuse rim thinning	
Large	• Round shape with light 360 PPA and saucerized appearance		• Tilted with heavy PPA, diffuse rim thinning, and visible lamina cribrosa	

Table 2. **Preliminary Logistic Regressions**

	Small Optic Discs		Large Optic Discs	
Covariate	**OR***	**95% CI**	**OR***	**95% CI**
No. eyes	*219*		*165*	
Sex				
Male	Reference	Reference	Reference	Reference
Female	1.65	0.81, 3.40	0.96	0.33, 2.85
Race / ethnicity				
White	Reference	Reference	Reference	Reference
Asian	2.49	0.65, 12.01	0.12	0.01, 0.77
Black	4.26	0.60, 85.01	0.56	0.10, 2.58
American Indian or Alaskan Natives	–	–	–	–
Other	0.40	0.08, 1.48	0.37	0.05, 1.95
Glaucoma type				
POAG	Reference	Reference	Reference	Reference
Pseudoexfoliative	0.59	0.02, 15.23	0.53	0.03, 4.61
Steroid-Induced	–	–	–	–
Congenital	–	–	0.27	0.04, 1.16
Angle Closure	0.02	0.00, 0.12	1.60	0.06, 42.54
Pigment Dispersion	–	–	–	–
Other	–	–	–	–
Cardiovascular disease (Diabetes, HTN, CVD, hyperlipidemia)	0.53	0.19, 1.36	0.46	0.35, 3.64
Vasospastic phenotype (Hypotension, migraines, Raynaud's syndrome)	1.05	0.24, 4.64	3.61	0.03, 5.61
Obesity	0.12	0.10, 0.66	–	–
Any smoking history	0.51	0.23, 1.09	0.48	0.1, 1.8

* Odds ratio (OR) represents odds of GRI < -3, adjusted for all covariates in Table 2
– Statistically unstable due to small sample sizes

Results

- Total population: N = 384
  - Small disc eyes: N = 219
  - Large disc eyes: N = 165
- Mean GRI:
  - Small discs: -7.6
  - Large discs: -8.8
- Potential clinical factors associated with reduced risk of progression include obesity in eyes with small discs and Asian race/ethnicity in eyes with large discs
- On review of optic disc photos, we identified unique features of optic disc morphology in glaucomatous eyes with small vs. large discs, as well as with non-progressive vs. progressive VF deterioration, as modeled by GRI
- Disc characteristics associated with progression in small and large discs include:
  - Fast progressors – Tilt and PPA
  - Slow progressors – Round and lack of PPA

Conclusions & Future Directions

- Morphologic factors of the optic disc that are potentially associated with fast progression include tilt and PPA
- Clinical and morphological factors associated with slow progression include round shape and lack of PPA, as well as obesity in small discs and Asian race/ethnicity in large discs
- Chart review is ongoing, to culminate in a final cohort of 777 eyes (427 small discs, 350 large discs)
- We aim to integrate our findings to identify and describe clinical illustrations of phenotypic subtypes, which may be key to elucidating and isolating the diverse mechanisms underlying glaucoma, as well as guiding diagnosis and individualized treatment
- Identification of patients who display identifiable glaucoma phenotypes should alert clinicians to the possibility of fast rates of functional deterioration, allowing for timely intervention with appropriately aggressive treatments that may prevent further irreversible vision loss

References

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