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Insights in neuro-ophthalmology disorders 2023

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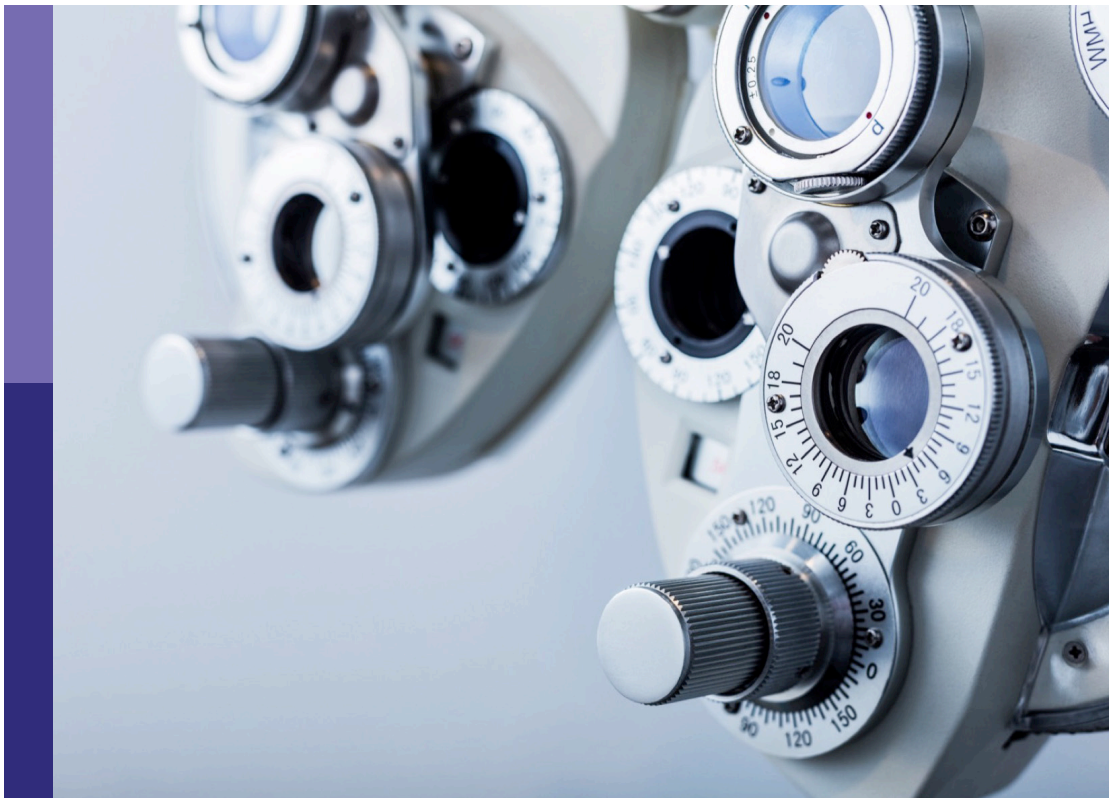

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Insights in neuro-ophthalmology disorders: 2023

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BRIEF RESEARCH REPORT
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Factors Associated With Adherence to Outpatient Follow-Up in Patients With Idiopathic Intracranial Hypertension (IIH)

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Idiopathic intracranial hypertension (IIH) is a chronic condition characterized by raised intracranial pressure of undetectable origin, that causes morbidity due to debilitating headaches and vision loss. Continuity of outpatient care is important to monitor for permanent vision loss, manage symptoms and limit emergency care. The purpose of this retrospective study was to identify factors associated with neuro-ophthalmology follow-up appointment completion among patients with IIH at a US academic medical center in order to establish evidence-based interventions to improve adherence patterns. Included are 111 completed or no-show neuro-ophthalmology return outpatient appointments by 23 subjects with IIH. Generalized estimating equation models were used to assess association between appointment completion status and factors previously shown to be associated with appointment adherence. Appointments were more likely to be completed during the summer (p=0.08) and by subjects with headache symptoms (p=0.06), however none of the patient factors reached statistical significance. Completed and no-show appointments did not differ by subject demographic or insurance factors. Further studies are needed to identify risk factors for lack of appointment adherence by patients with IIH, particularly those amenable to intervention, in order to improve continuity of care for IIH.

Keywords: idiopathic intracranial hypertension, outpatient care, resource utilization, follow-up compliance, sociodemographic factors, appointment adherence

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INTRODUCTION

Idiopathic intracranial hypertension (IIH) is a disorder of increased intracranial pressure (ICP), classically occurring in overweight women of childbearing age (1). As per its name, the cause of IIH is unknown, and diagnosis requires confirmation of lack of secondary causes for high ICP such as brain tumor, cerebral venous sinus thrombosis and meningitis. Heterogeneity of IIH is seen with a wide range of visual outcomes including disease progression in some patients despite treatment

compliance, thus necessitating escalation of therapy and surgical intervention in some cases (2–4). Furthermore, IIH is a chronic condition that can worsen following periods of stability, thereby warranting longitudinal follow-up to optimize outcomes (5). This highlights the importance of ongoing longitudinal follow-up in preventing progression and sudden deterioration in visual outcomes.

Successful longitudinal care requires adherence to ongoing outpatient appointments and the ability to predictably identify those at risk of being lost to follow up. To establish evidence-based interventions that improve follow-up adherence, it is necessary to first identify factors associated with it. A host of internal and external factors influence adherence behavior, and thus shape health outcomes in return. These can be organized into five major domains: socioeconomic factors, health system-related factors, therapy-related factors, condition-related factors, and finally, patient-related factors (6). Accordingly, the goal of the present study was to identify factors associated with completion of recommended outpatient follow-up appointments by IIH patients.

METHODS

This is a retrospective study of adult patients with IIH followed by an urban academic neuro-ophthalmology service in the University of Illinois Hospital & Health Sciences System (UIH). This project was reviewed by the University of Illinois at Chicago (UIC) institutional review board under expedited procedures with a waiver of informed consent and waiver of HIPAA authorization.

Subjects were identified by chart review. Adult subjects (≥21 years old) with confirmed IIH diagnosis, who completed at least one outpatient neuro-ophthalmology appointment between June to September 2014, were included. For these subjects, all neuro-ophthalmology follow-up encounters between 2012-2015 were abstracted. Canceled, rescheduled, and patient-initiated encounters were excluded. The reason for these exclusions was to focus on patient adherence to provider recommended follow-up. The included encounters were classified as completed or no show.

Subject demographic factors including age, race/ethnicity, zip code, insurance status (private or government) were abstracted from the medical record. Residential distance from the clinic was calculated through Google Maps, using the subject's zip code to measure the shortest driving distance from home to UIH. Health status was determined based on prescription of medications for diseases other than IIH.

Appointment factors were abstracted from the electronic scheduling system and medical record, and included: time of day (morning or afternoon), season (winter, spring, summer, fall), follow-up time from last completed appointment (1 week, 1 month, 2 months, 3 months, 6 months), whether subject is receiving treatment for IIH, IIH medication change at or since prior appointment, and symptoms at last appointment (headache or not).

Appointment status was the primary outcome. Generalized Estimating Equation (GEE) analysis was applied to model this as a dichotomous outcome (no show *vs*. completed) using logit link with subject as a grouping variable to account for within subject correlations. Unadjusted analysis was performed for each considered subject and appointment factor. Analysis was performed using SPSS 26 (IBM Inc).

RESULTS

Twenty-three subjects with IIH (mean age 39, all female, 14 (60%) Black non-Hispanic, 0-66 miles between residence and clinic, 19 (82%) on IIH medication, 11 (47%) with Medicaid insurance) had 321 appointments scheduled between 2012-2015. Two hundred and ten were excluded for being cancelled, rescheduled, initial consultation, patient-initiated, visual field only or undocumented appointments. The remaining 111 appointments were categorized as completed (n=92, 83%, range 1-12 per patient) or no-show (n=19, 17%, range 0-5 per patient) visits.

None of the patient factors were associated with adherence to outpatient appointments. Appointments scheduled in the summer season had higher adherence, and those with 1 month follow-up interval had lower adherence, but these did not reach statistical significance. Subjects with active headache had better follow-up, but this did not reach statistical significance. There was no association between other appointment factors (time of day, season, follow-up time, treatment status, mediation changes, symptoms reported) and outpatient appointment adherence among IIH patients (**Table 1**).

DISCUSSION

The understanding of factors associated with continuity of outpatient care for those with IIH is important for designing interventions to improve outcomes in this chronic disease. Secondary benefits would include more cost-effective care and reduced overall resource utilization (7). Towards this end, we present a study assessing factors related to outpatient follow-up adherence in patients with IIH, receiving care at an urban academic medical center in the United States.

Our study of established IIH patients in a neuro-ophthalmology practice did not identify intervenable factors associated with outpatient follow-up completion. Trends for seasonal effects existed, with compliance being better in the summer than the winter, possibly attributable to the weather in Chicago or fewer work/school scheduling conflicts. Follow-up completion was better in subjects with persistent symptoms. However, neither of these factors reached statistical significance, perhaps related to sample size. Ongoing study is critical given the importance of outpatient follow-up to allow management of chronic conditions. In other diseases correlations between outpatient adherence and cultural, sociodemographic and psychosocial factors have been demonstrated (8, 9).

TABLE 1 | Distribution of patient and appointment factors by attendance, and association with non-adherence.

Factors	% No-show (n = 19)	% Completed (n = 92)	Odds Ratio (95% CI)*	P-value*
Age in years (Mean ± SD)	41.7 ± 8.6	43.0 ± 10.6	0.99 (0.94-1.04)	0.64
Race/ethnicity:			1.48 (0.43-5.10)	0.53
Black-non-Hispanic	63%	72%		
Distance from clinic (miles)	0-66	0-23	1.032 (0.98-1.09)	0.28
Insurance status: Public aid	26.3%	32.6%	1.36 (0.61-3.00)	0.46
Health status: Receiving meds	94.7%	84.6%	0.31 (0.06-1.65)	0.17
Time of day: AM	68%	66%	0.91 (0.32-2.55)	0.89
Season				
Spring	26%	19%	1.14 (0.32-4.02)	0.84
Summer	16%	33%	3.16 (0.86-11.60)	0.08
Fall	26%	27%	1.58 (0.49-5.06)	0.44
Winter	32%	21%	ref	
Follow-up time				
1-2 weeks	5%	12%	ref	0.06
1 month	42%	25%	0.26 (0.06-1.08)	0.40
2 months	11%	10%	0.41 (0.05-3.23)	0.73
3-4 months	21%	35%	0.73 (0.12-4.55)	0.33
6 months	21%	18%	0.39 (0.06-2.62)	
IIH treatment: Yes	79%	72%	0.68 (0.18-2.61)	0.57
Recent IIH med change: Yes	47%	39%	0.71 (0.38-1.51)	0.38
IIH symptoms (headache): Yes	53%	76%	2.82 (0.96-8.30)	0.06

**Odds ratio and p-values calculated using GEE models accounting for within subject correlation.*

Further research is needed to identify patient-related and health-system factors that are associated with follow-up care in IIH so that patients at risk of poor follow-up can be identified and appropriately managed. As an example of what might be accomplished, one study evaluating follow-up patterns in HIV-seropositive patients led to proposed interventions to minimize sociodemographic barriers to appointment adherence in order to promote optimal management of disease progression (8). Similarly, literature surrounding diabetes follow-up asserts the influence of psychosocial factors in chronic disease management, highlighting that patients with attachment styles characterized by low levels of collaboration were more likely to miss appointments than those with secure attachment styles (10). It is worth noting that many of those with poor follow-up compliance will naturally be the most challenging to access during observational research studies. Thus, it is important to critically evaluate solutions drawn from studies that focus on more accessible populations, and contextualize them in terms of those most lost to care (11, 12). Future research regarding follow-up disparities in IIH patients will need to be more encompassing of underrepresented populations with greater likelihood of experiencing the greatest health needs.

Intentional *versus* unintentional nonadherence would be another notable avenue to assess as it has shown importance in research concerning compliance of glaucoma patients with ocular hypotensive therapies (13). Additionally, identifying factors affecting adherence in patients from different genders and cultural backgrounds may be significant to understanding follow-up patterns in patients with IIH, majority of whom are females. In a recent study, beliefs about glaucoma treatment were predictive of adherence in patients of western cultures, suggesting possible improvement of adherence patterns through examination of patient concerns and illness perceptions (14). Finally, a thorough assessment of tailored interventions and their impact on medical adherence and health outcomes would strengthen their implementation to help patients with IIH achieve better follow-up.

Our study is based on the assumption that longer follow-up leads to better health outcomes. Though this has not been formally evaluated in patients with IIH, a recent prospective study demonstrated an association between changes in IIH care prompted by the COVID-19 lockdown and changes in management (15). Moreover, established outpatient care has been associated with better outcomes in other chronic disease conditions. In a study of outpatient diabetes management, consistent appointment attendance was a strong predictor of successful disease control (16). Similarly, a case study examining attendance at outpatient clinics identified appointment nonadherence as a significant disadvantage in the provision of effective medical care (17). A literature review looking at nonadherence in chronic disease conditions identified numerous consequences in medical care provision impacting individual patients and overall health systems (18). These included increased wait times, strained patient–provider relationships, and increased system costs in addition to accumulative negative impacts on patient health, which limit continuity of care and disrupt management plans (19–21). Such conditions delay necessary treatment, leaving patients at an increased vulnerability for the development of serious medical complications. Rigorous study is needed to demonstrate the importance of outpatient specialty care in improving IIH outcomes while reducing costs.

Our findings are not without limitations. Generalizability of our study is limited by its retrospective nature and restriction to a single center, thereby excluding geographic variability and possible relevant care obtained from outside providers. We had a small sample size which was driven in part by restriction to subjects with a confirmed IIH diagnosis only. Future work could include a larger sample size to reveal statistically significant

associations and enable subgroup analyses. We were unable to capture cultural, sociodemographic, and psychosocial factors, which as discussed earlier, pose important considerations for adherence and follow-up. Future studies may consider directly exploring reasons for poor adherence through the use of patient questionnaires or interviews. Additionally, it would be worthwhile to revisit patients with cancelled and rescheduled appointments, who were originally excluded in our inclusion criteria, to assess whether adherence to follow-up care took place.

In conclusion, our pilot study did not identify specific factors upon which to intervene to establish outpatient care and maintain appointment compliance. Thus, further research is required to better understand factors associated with continuity of care for patients with IIH in order to facilitate a shift to longitudinal outpatient care. Ultimately, this would serve the purpose of continued follow-up for optimal management of IIH, as well as the potential to minimize IIH-related healthcare costs. One particularly interesting approach would be to map out the sequence and stages of care in patients with IIH, such as diagnosis, management and maintenance, in order to identify patterns, their possible causes and appropriate interventions to implement.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Illinois at Chicago (UIC) institutional review board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conceptualization, RA and HM. Methodology, AS, and HM. Formal analysis, AS and HM. Investigation, AS and HM. Resources, HM. Data curation, AS. Writing—original draft preparation, RA. Writing—review and editing, RA and HM. Visualization, RA, AS, and HM. Supervision, HM. Project administration, HM. All authors contributed to the article and approved the submitted version.

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Peripapillary Choroidal Vascularity and Visual Correlates in Non-Arteritic Anterior Ischemic Optic Neuropathy Using Swept-Source Optical Coherence Tomography

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Introduction: The peripapillary choroid shares a blood supply with and is directly apposed to the optic nerve, and therefore may contribute to the pathogenesis of non-arteritic anterior ischemic optic neuropathy (NAION). Prior studies evaluating peripapillary choroidal thickness (PCT) or choroidal vascularity index (CVI; the ratio of the perfused area to total choroid area) have produced mixed results. None investigated the relationship between PCT and CVI or demonstrated functional correlates. We hypothesized that greater PCT and lower CVI would correlate with visual function in patients presenting with NAION.

Methods: Seventeen eyes with NAION (9 acute, 8 non-acute) and 6 unaffected "fellow" eyes in 13 patients, and 18 eyes in 18 age-matched control subjects were imaged using swept-source optical coherence tomography (SS-OCT) prospectively between 2017-2018. Mean PCT and CVI measurements were compared across groups and with respect to corresponding automated perimetric performance at the same visit.

Results: Analysis of variance showed significantly greater PCT (NAION: 278 ± 65 μm, Fellow: 221 ± 50 μm, Control: 158 ± 27 μm, $p<0.001$) and lower CVI (NAION: 0.35 ± 0.03, Fellow: 0.35 ± 0.04, Control: 0.38 ± 0.02, $p<0.005$) in patients with NAION compared to control subjects. Bonferroni-corrected pairwise comparisons showed greater PCT and lower CVI in NAION-affected eyes compared to control eyes (p values<0.008), and no significant differences in PCT or CVI between NAION and fellow eyes (p values>0.06). PCT was negatively correlated with CVI among unaffected fellow eyes (r=-0.8, $p<0.05$), but not among acute NAION eyes (r=-0.1, $p>0.7$), non-acute NAION eyes (r=0.1, $p>0.7$), or controls (r=-0.3, $p>0.2$). Nasal CVI was positively correlated with mean deviation scores in non-acute NAION (r=0.8, $p<0.02$), but not among fellow unaffected eyes (r=0.8, $p>0.05$)

or acutely affected NAION eyes (r=-0.3, p>0.4). Mean and temporal PCT correlated with pattern standard deviation scores among unaffected fellow eyes (r=0.8, p<0.04; r=0.9, p<0.03), but not among acute NAION eyes (r=-0.2, p>0.5; r=-0.1, p>0.7) or non-acute NAION eyes (r=0.1, p>0.7; r=0.05, p>0.9).

Conclusion: NAION and unaffected fellow eyes demonstrate increased choroidal thicknesses and reduced vascular density. Perimetric performance is directly associated with vascular density among non-acutely affected eyes with NAION. Ongoing work will provide further insights into these structure-function relationships with pathogenic and pathophysiologic relevance.

Keywords: non-arteritic anterior ischemic optic neuropathy (NAION), peripapillary choroidal thickness, peripapillary choroidal vascularity, swept-source OCT (SS-OCT), visual correlation

INTRODUCTION

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common acute optic neuropathy in adults over age 50 and causes sudden, painless unilateral vision loss. Patients with NAION experience long-term visual impairment and visual field deficits. The pathogenesis of NAION is not well understood but may involve vascular insufficiency to the retrolaminar optic nerve, which is supplied by the short posterior ciliary arteries (1). A small, crowded disc ("disc at risk") may directly convey an anatomic vulnerability to vascular insufficiency that precipitates NAION (2).

The low-resistance peripapillary choroid shares a blood supply with and is directly apposed to the optic nerve, and therefore may contribute to the pathogenesis of NAION (3). Prior OCT studies evaluating peripapillary choroidal thickness (PCT) and choroidal vascular index (CVI; the ratio of the vascular area to total choroid area) have produced mixed results (3–9). Four studies have shown increased PCT in NAION eyes compared to control eyes (3, 5, 6, 9), one study found decreased PCT in NAION (4), and one study reported no difference (8). With regards to choroidal vascularity, one study found decreased CVI in NAION (7). Notably, no prior study has investigated the potential association between PCT and CVI. This relationship may be important because PCT is not an ideal surrogate for vascular supply, as it captures stromal and interstitial components in addition to the vasculature. Furthermore, no study has demonstrated visual function correlates of PCT or CVI differences.

Swept-source optical coherence tomography (SS-OCT) utilizes a faster scanning speed and longer-wavelength laser compared to spectral-domain OCT (SD-OCT) devices, thereby providing higher resolution imaging of the choroid (10). We aimed to compare PCT and CVI between NAION eyes, unaffected "fellow" eyes, and healthy control eyes. We hypothesized that SS-OCT would reveal greater PCT and lower CVI among NAION eyes that correlate with visual function. In addition, we hypothesized that choroidal thickness may be inversely associated with vascularity if both structural and vascular changes are involved in NAION pathogenesis.

MATERIALS AND METHODS

Participants

The prospective, observational study was approved by the institutional review board of Massachusetts Eye and Ear, and informed consent was obtained from all participants. All procedures adhered to the tenets of the Declaration of Helsinki and Health Insurance Portability and accountability Act regulations.

Adults with a clinical diagnosis of acute or non-acute NAION in one or both eyes, unaffected fellow eyes, and age-matched controls (closest match by age within 2 years) were imaged between October 2017 and December 2018. Consecutive patients with NAION presenting to protocol providers during the study period were identified, screened, and enrolled through the Neuro-ophthalmology service. Only patients with an unambiguous diagnosis of NAION assigned by an experienced neuro-ophthalmologist were included. Clinical features of NAION include sudden, painless, unilateral vision loss, relative afferent pupillary defect, optic disc edema on fundoscopy, visual field defects consistent with NAION, normal ESR/CRP levels, no signs or symptoms of giant cell arteritis, and resolution of disc edema within 2 months. Acute NAION was defined by disc edema in eyes within 3 months since onset of visual loss. Two patients with acute NAION were subsequently enrolled in a randomized, double-masked clinical trial of QPI-1007 (NCT02341560). No patients received any intervention or treatment for NAION prior to imaging and functional visual assessments. No other patients received treatment for the acute NAION episode. Control eyes were fellow eyes of patients with history of unilateral retinal detachment enrolled through the Retina service. Exclusion criteria included image quality index <30 (range 0-100) according to the device's default settings, glaucoma, and concomitant chorioretinal or neurologic disease.

Study Protocol

All participants underwent a complete ophthalmic examination, including Snellen best-corrected visual acuity (BCVA) measurement, slit-lamp examination, intraocular pressure (IOP) measurement, and dilated fundus examination.

Participants were imaged using a SS-OCT (DRI Triton, Topcon, Japan) that uses a laser at a central wavelength of 1,050 nm and scanning speed of 100 kHz. The 12- x 9-mm 3D Volume scan protocol ("3D Wide") was used with automated segmentation. Automated perimetry (Humphrey, 24-2 SITA standard) was performed on the day of OCT analysis in all cases. Perimetric data were not included if the reliability parameters provided by the test paradigm exceeded 30% fixation losses, 20% false positives, or 20% false negatives; however, SS-OCT data were still included for assessment of PCT and CVI. Snellen acuities were converted to logMAR for statistical analyses.

Quantitative Analysis of Images

Topcon IMAGEnet 6 software was used to obtain PCT values. For each fundus image, a superimposed 3.4-mm diameter RNFL-12 grid displaying PCT values for each of 12 peripapillary sectors was manually centered on the optic nerve (**Figure 1A**). For each SS-OCT B-scan, manual segmentation of the choroid-scleral

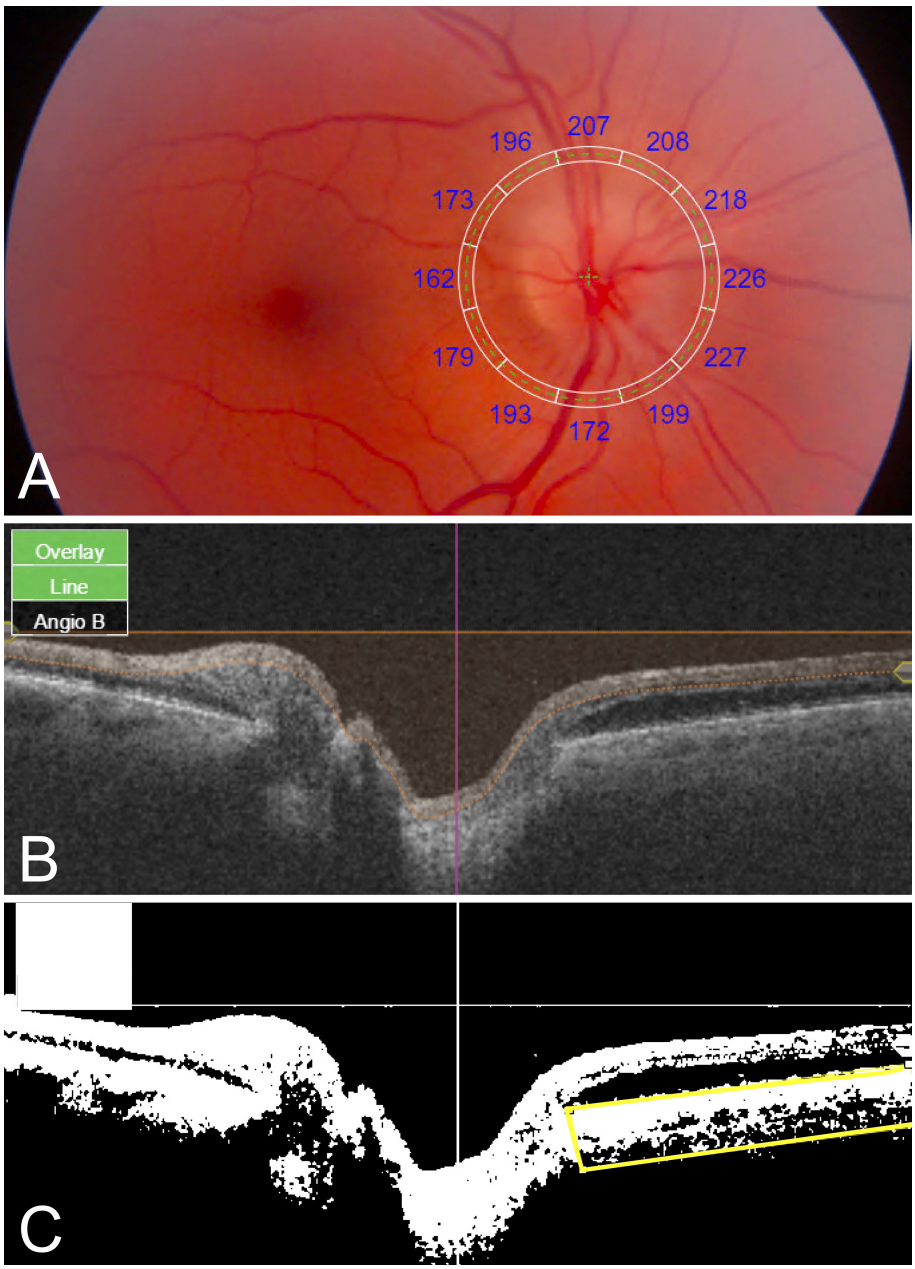

FIGURE 1 | Quantitative PCT and CVI measurements using SS-OCT 12- x 9-mm images. **(A)** Fundus image with superimposed grid with sectoral PCT values. **(B)** Original SS-OCT B-scan. **(C)** Binarized SS-OCT B-scan image with manually segmented choroid (yellow box); CVI was calculated as luminal area/total area black, luminal area; white, stromal/interstitial area.

interface was performed to correct segmentation errors. IMAGEnet 6 necessitates investigator viewing of the fundus image for centration, revealing the appearance of the optic disc to the investigator; thus, while manual segmentation was performed without regard for eye/patient group, it could not be performed in a masked fashion. Superior, inferior, nasal, and temporal quadrant PCTs were calculated by averaging the 3 peripapillary sectors in the corresponding quadrant. Mean PCT was calculated as the average of the 12 sectoral PCT values.

ImageJ/Fiji software (National Institutes of Health, Bethesda, MD) was used to determine CVI in the peripapillary area extending 6mm radially from the optic nerve. SS-OCT B-scans were downloaded from IMAGEnet 6. Using an adapted CVI protocol (11), original B-scan images (**Figure 1B**) were binarized, the peripapillary choroid was manually segmented using the polygonal selection tool, and the segmented ROI was isolated (**Figure 1C**). CVI was calculated as the luminal area as a proportion of the total area (luminal area plus stromal area). For each patient, one horizontal B-scan centered on the optic disc was used to calculate nasal and temporal CVI. Mean CVI was calculated as the average of nasal and temporal CVI values.

Statistical Methods

Statistical analyses were performed using R software (R Foundation for Statistical Computing). Analysis of variance was used to determine the effect of group (NAION eyes, fellow eyes, control eyes) on PCT and CVI. Bonferroni-corrected pairwise comparisons were used to compare PCT and CVI between groups and adjust for multiple comparisons. Pearson correlations were used to determine the relationship between PCT and CVI within groups, as well as the relationship between structural (PCT, CVI) and corresponding automated perimetry performance at the same visit (mean deviation, pattern standard deviation). All statistical tests were 2-sided, and p values <0.05 were considered statistically significant.

RESULTS

A total of 17 NAION eyes (9 acute, 8 non-acute) and 6 unaffected fellow eyes of 13 patients, and 18 eyes of 18 age-matched control subjects were included. Three affected eyes of patients with NAION were excluded due to poor image quality or artifacts. Patients with NAION were 62.8 ± 9.4 years of age on average (± SD) and presented with a mean BCVA of 0.12 ± 0.3 logMAR (Snellen 20/25) and IOP of 15.0 ± 2.2 mmHg (**Table 1**). Among the 8 non-acute eyes with NAION, the mean duration after the acute episode was 2.0 ± 2.5 years. Control participants had a mean age of 60.5 ± 5.5 years, mean BCVA of 0.02 ± 0.10 logMAR, and mean IOP of 15.8 ± 3.0 mmHg. Pairwise comparisons demonstrated no statistically significant differences in age, sex, BCVA, and IOP across groups (p values>0.3).

No difference in PCT was found between acute and non-acute eyes with NAION (p>0.07). Analysis of variance showed significantly increased PCT in patients with NAION compared to control subjects (NAION: 278 ± 65 μm, Fellow: 221 ± 50 μm, Control: 158 ± 27 μm, p<0.001) (**Figure 2**). In addition, the NAION group demonstrated decreased CVI compared to controls (NAION: 0.35 ± 0.03 μm, Fellow: 0.35 ± 0.04 μm, Control: 0.38 ± 0.02 μm, p<0.005). Bonferroni-corrected pairwise comparisons revealed that increased PCT was present in all quadrants (superior, inferior, nasal, temporal) in affected NAION eyes compared to controls (p values<0.001) (**Table 1** and **Figure 3A**). Unaffected, fellow eyes also demonstrated increased mean and temporal PCT compared to controls (p values<0.04); this difference was not statistically significant for the superior, inferior, and nasal quadrants (p values>0.06). No differences in PCT were observed between NAION and fellow eyes (p values>0.06).

NAION eyes exhibited decreased mean CVI compared to controls (p<0.008) (**Table 1** and **Figure 3B**). Sectoral analyses revealed this difference in both nasal and temporal quadrants

TABLE 1 | Demographic, Ocular, and SS-OCT Characteristics Among NAION Eyes, Fellow Eyes, and Control Eyes.

	NAION Eyes (n = 17)	Fellow Eyes (n = 6)	Control Eyes (n = 18)	P Value, NAION *vs.* Control	P Value, Fellow *vs.* Control	P Value, NAION *vs.* Fellow
Age, years	62.8 ± 9.4	59.2 ± 9.0	60.5 ± 5.5	>0.99	>0.99	>0.99
Sex, male (%)	13 (76.5)	6 (100)	13 (72.2)	>0.99	0.50	0.73
BCVA, logMAR	0.12 ± 0.3	-0.02 ± 0.1	0.02 ± 0.1	0.30	>0.99	0.35
IOP, mm Hg	15.0 ± 2.2	15.6 ± 2.9	15.8 ± 3.0	>0.99	>0.99	>0.99
HVF mean deviation, dB	-13.1 ± 7.3	-0.5 ± 1.5	N/A	N/A	N/A	<0.001*
HVF pattern standard deviation, dB	11.7 ± 4.7	1.5 ± 0.3	N/A	N/A	N/A	<0.001*
Mean PCT, μm	278.0 ± 65.2	221.4 ± 50.4	157.5 ± 26.9	<0.001*	0.028*	0.063
Superior quadrant PCT, μm	278.8 ± 77.0	215.6 ± 61.7	150.2 ± 27.0	<0.001*	0.063	0.08
Inferior quadrant PCT, μm	263.3 ± 90.5	205.5 ± 58.9	135.8 ± 36.2	<0.001*	0.10	0.23
Nasal quadrant PCT, μm	278.1 ± 58.8	226.1 ± 51.1	175.9 ± 27.7	<0.001*	0.082	0.069
Temporal quadrant PCT, μm	291.7 ± 76.0	238.6 ± 50.8	167.9 ± 33.5	<0.001*	0.038*	0.173
Mean CVI	0.35 ± 0.03	0.35 ± 0.04	0.38 ± 0.02	<0.008*	0.068	>0.99
Nasal CVI	0.38 ± 0.03	0.38 ± 0.02	0.40 ± 0.02	0.035*	0.65	>0.99
Temporal CVI	0.33 ± 0.04	0.32 ± 0.06	0.37 ± 0.04	0.048*	0.095	>0.99

SS-OCT, swept-source optical coherence tomography; NAION, non-arteritic anterior ischemic optic neuropathy; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; IOP, intraocular pressure; HVF, Humphrey visual field; PCT, peripapillary choroidal thickness; CVI, choroidal vascularity index.

Values presented as mean ± standard deviation unless otherwise noted.

**Indicates P<0.05, Bonferroni-corrected pairwise comparisons.*

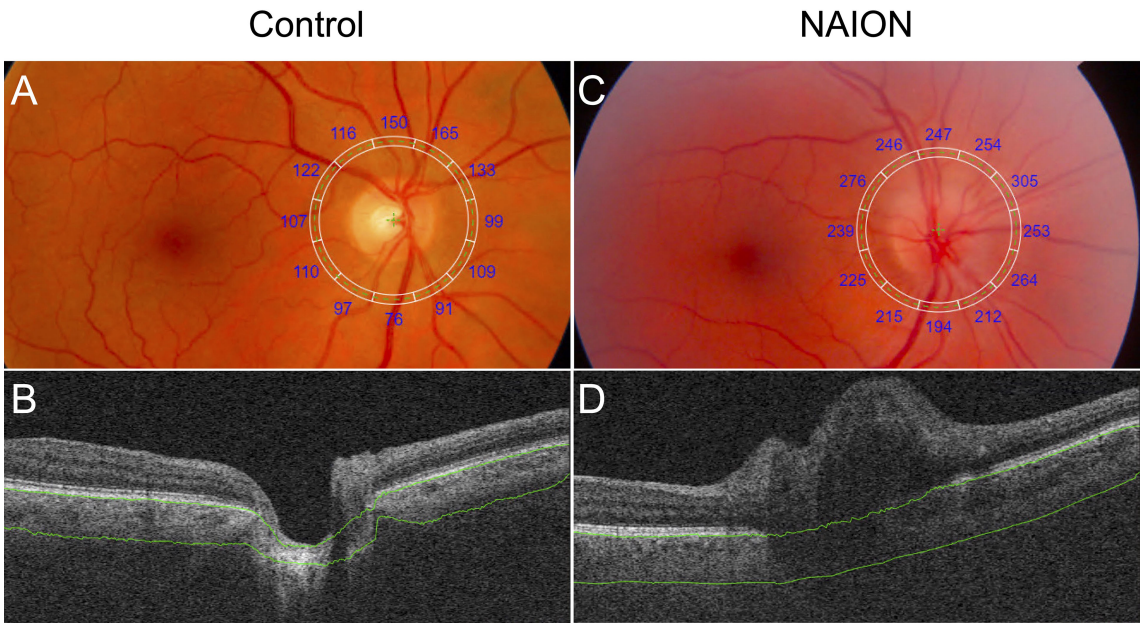

FIGURE 2 | Comparison of PCT in a control eye and an eye with NAION. **(A)** Fundus image with superimposed grid with sectoral PCT values **(A)** and SS-OCT B-scan **(B)** of a control eye show decreased PCT compared to the fundus image **(C)** and SS-OCT B-scan **(D)** of an eye with NAION. Segmentation of Bruch's membrane and the choroid-sclera interface are shown in green.

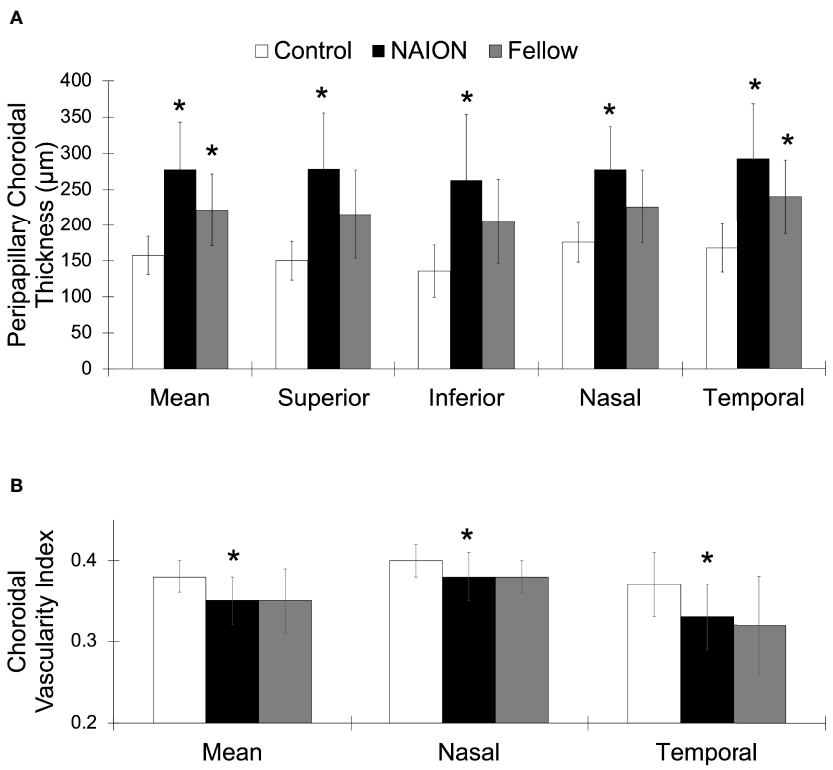

FIGURE 3 | Greater PCT and lower CVI in NAION compared to control eyes. **(A)** Mean and sectoral PCT values. **(B)** Mean, nasal, and temporal CVI values. NAION (white), fellow eye (black), and control (gray) groups. *Signifies $p<0.05$ compared to control group.

(p values<0.05). Comparing CVI measures of fellow eyes to those of controls yielded margins that bordered on statistical significance (p values>0.06). CVIs of NAION and fellow eyes were similar (p values>0.9).

Mean PCT negatively correlated with mean CVI among unaffected fellow eyes (r=-0.8, p<0.05) (**Figure 4A**), but not among acute NAION eyes (r=-0.1, p>0.7), non-acute NAION eyes (r=0.1, p>0.7), or controls (r=-0.3, p>0.2).

We next evaluated for structure-function relationships through analysis of perimetric data. Nasal CVI was positively correlated with mean deviation scores among non-acute NAION eyes (r=0.8, p<0.02), but not among acute NAION eyes (r=-0.3, p>0.4) (**Figure 4B**). The nasal CVI-mean deviation relationship among unaffected eyes bordered on statistical significance (r=0.8, p<0.06). Mean PCT correlated with pattern standard deviation scores among unaffected fellow eyes (r=0.8, p<0.04) (**Figure 4C**), but not among acute NAION eyes (r=-0.2, p>0.5) or non-acute NAION eyes (r=0.1, p>0.7). Similarly, temporal PCT correlated with pattern standard deviation scores among unaffected fellow eyes (r=0.9, p<0.03), but not among acute NAION eyes (r=-0.1, p>0.7) or non-acute NAION eyes (r=0.05, p>0.9).

DISCUSSION

We found thicker peripapillary choroids and reduced vascularity in eyes affected by NAION, and greater vascularity corresponded with relatively better perimetric performance in non-acute NAION eyes. To our knowledge, this is the first study to assess the relationship between PCT and CVI, and to identify a potential choroidal vascular structure-function correlate in NAION. Thus, these data signify important anatomic factors identifiable with OCT that may carry prognostic implications in NAION.

Several previous studies have investigated PCT in NAION using OCT (**Table 2**). Using the Cirrus SD-OCT, García-Basterra reported decreased PCT in 37 non-acute NAION eyes compared to healthy controls (4). Using the extended depth of imaging SD-OCT (Spectralis, Heidelberg), three groups found increased PCT in NAION and one study reported no difference in PCT between NAION and control eyes (3, 5, 8, 9). With the Triton SS-OCT (used in this study), Pérez-Sarriegui observed greater PCT whereas Guduru reported decreased CVI (6, 7). This study is consistent with the majority of prior studies that found thicker choroids and reduced vascularity in NAION using OCT. The conflicting results

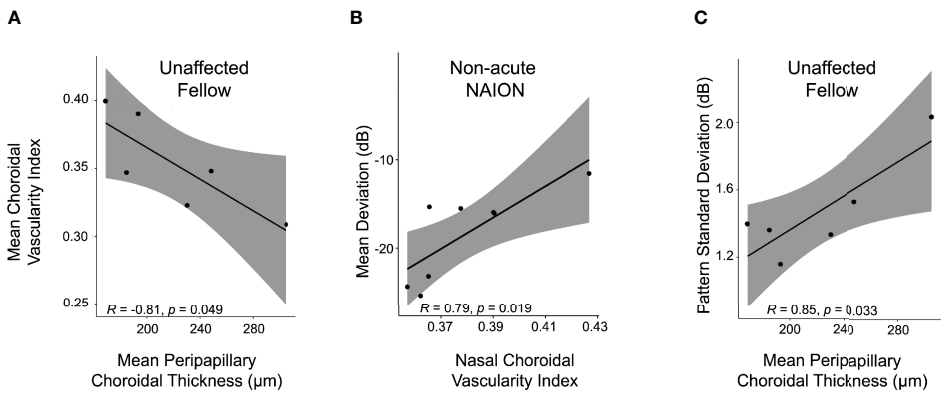

FIGURE 4 | PCT/CVI relationship and structure-function correlate in NAION. **(A)** PCT correlates inversely with CVI in unaffected fellow eyes. Higher PCT corresponded with lower CVI among unaffected fellow eyes (r=-0.8, p<0.05), but not among acute NAION eyes (r=-0.1, p>0.7), non-acute NAION eyes (r=0.1, p>0.7) or controls (r=-0.3, p>0.2). **(B)** Nasal CVI correlated directly with perimetric performance in non-acute NAION (r=0.8, p<0.02), but not in acute NAION (r=-0.3) or fellow eyes (r=0.8, p values ≥0.06). **(C)** Mean PCT correlated directly with pattern standard deviation scores among unaffected fellow eyes (r=0.8, p<0.04), but not among acute NAION eyes (r=-0.2, p>0.5) or non-acute NAION eyes (r=0.1, p>0.7).

TABLE 2 | Previous OCT studies investigating the peripapillary choroid in NAION.

Study (first author, year)	*n*, NAION eyes	OCT Name	OCT Type	PCT*	CVI*	Identified Visual Correlates?
García-Basterra (2016) (4)	37 (37 non-acute, 19 fellow, 38 control)	Cirrus	SD-OCT	↓	N/A	No
Fard (2015) (5)	30 (30 non-acute, 30 fellow, 25 control)	Spectralis	SD-OCT	↑	N/A	No
Nagia (2016) (3)	20 (20 non-acute, 10 fellow, 102 control)	Spectralis	SD-OCT	↑	N/A	No
Jiang (2016) (8)	44 (19 acute, 25 non-acute, 44 fellow, 60 control)	Spectralis	SD-OCT	↔	N/A	No
Nikkhah (2020) (9)	38 (38 acute, 38 fellow, 74 control)	Spectralis	SD-OCT	↑	N/A	No
Pérez-Sarriegui (2018) (6)	29 (29 non-acute, 21 fellow, 29 control)	Triton	SS-OCT	↑	N/A	No
Guduru (2019) (7)	20 (20 acute, 20 fellow, 40 control)	Triton	SS-OCT	N/A	↓	No
Current Study	17 (9 acute, 8 non-acute, 6 fellow, 18 control)	Triton	SS-OCT	↑	↓	Yes

PCT, peripapillary choroidal thickness; CVI, choroidal vascularity index; NAION, non-arteritic anterior ischemic optic neuropathy; SD-OCT, spectral-domain optical coherence tomography; SS-OCT, swept-source optical coherence tomography.

**NAION compared to controls (↑, Increased; ↓, decreased; ↔, no difference; N/A, did not assess).*

on PCT may be contributed by a number of factors. Studies using SD-OCT relied on manual as opposed to automated segmentation, and SS-OCT has shown greater reproducibility in measuring choroidal thickness (12, 13). In addition, SS-OCT and SD-OCT have demonstrated differences in choroidal thickness measurements that limit comparability across devices (14, 15). Moreover, systematic differences in the control groups may also contribute to the discrepancies in PCT findings.

Structural SS-OCT findings reported herein may help elucidate the poorly understood pathogenesis of NAION in the context of previously posited mechanisms. Under the compressive or compartment syndrome theory, a thicker choroid may anatomically restrict the limited optic disc space in structurally crowded nerves and thus contribute to NAION (16, 17). More specifically, a thickened choroid may compress the prelaminar neural tissues to a point that exceeds capillary perfusion pressure, resulting in a positive feedback loop of ischemia and edema that extends to the laminar and retrolaminar space (3, 18, 19). Our results and others' indicating a greater PCT in NAION are consistent with this hypothesis. Notably, unaffected fellow eyes in patients with NAION had increased PCTs compared to controls, though this difference was restricted to mean and temporal quadrant PCTs in this study. A thicker choroid in the fellow eye of NAION patients supports an underlying structural predisposition, as fellow eyes are at significant risk of developing NAION (20). The fact that we found more prominent differences in the affected eye (and difference between affected and fellow eyes that bordered on statistical significance) may reflect why that eye was affected first. Another proposed mechanism involves direct ischemia to the retrolaminar portion of the optic nerve head. Consistent with this hypothesis, the reduced vascularity of the choroid observed in NAION eyes may reflect susceptibility to ischemia. Overall, our results support multiple hypotheses relating to the pathogenesis of NAION, possibly reflecting the multifactorial nature of this enigmatic disorder.

PCT and CVI were negatively correlated among unaffected fellow eyes, but not among acute NAION eyes, non-acute NAION eyes, or controls. It is unclear whether this finding reflects drivers and/or consequences of ischemia in eyes at risk for NAION, but the relationship was robust and clearly restricted to unaffected fellow eyes. Longitudinal studies are needed to determine if the observed PCT/CVI relationship is a reliable marker for the development of sequential NAION. Perimetric performance was directly associated with vascular density only in non-acute NAION. A parsimonious interpretation of this finding is that greater vascularity may be protective and/or promote recovery following a NAION attack. It is unclear what the potential relationship between choroidal vascularity and perimetric performance in fellow eyes may indicate. We would speculate that susceptibility to ischemia may be reflected in subtle differences in perimetric performance among pre-clinical NAION eyes. Longitudinal studies evaluating choroidal vascularity and choroidal thickness in unaffected fellow eyes of NAION patients is needed to determine if CVI or PCT can predict sequential NAION.

Our study's limitations include a relatively small number of usable NAION and fellow unaffected eyes due to SS-OCT imaging artifacts, segmentation error, and patient cooperation and fixation, all of which serve as barriers to obtaining high quality SS-OCT images. Additionally, acute and non-acute NAION were grouped together in this study given the limited sample of NAION cases, and peripapillary edema may alter PCT measurements in acute NAION. Furthermore, axial length and refractive error can influence OCT measures, but this information was not available for our NAION or control subjects. It is worth noting that the choroidal thickness measurement in our control group is similar to those reported elsewhere using SD-OCT and SS-OCT (3–6). Future prospective imaging studies should incorporate measurements of axial length and adjust accordingly to mitigate any potential confounding effects.

In conclusion, we show that NAION and unaffected fellow eyes demonstrate increased peripapillary choroidal thicknesses and reduced vascularity. Perimetric performance is directly associated with vascular density among non-acutely affected eyes with NAION. Longitudinal studies are needed to determine the clinical relevance of these structure-function relationships, both with regard to their applicability to neuro-ophthalmic practice and to provide further insights to the pathogenesis and pathophysiology of NAION.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional review board of Massachusetts Eye and Ear. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization: EL, JM, and EG. Data curation: EL, RK, and EG. Formal analysis: EL and EG. Investigation: EL and EG. Methodology: EL, RK, and EG. Project administration: JM and EG. Software: EL. Supervision: EL, JM, and EG. Validation: EL and EG. Visualization: EL and EG. Writing - original draft: EL. Writing - review and editing: EL, RK, JM, and EG.

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Conflict of Interest: JM: Alcon, Zeiss, Sunovion, Allergan, Genentech. EG: Luminopia, Inc (scientific advisor, equity, patent), Stoke Therapeutics, Inc (consultant).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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OPINION
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Non-Arteritic Anterior Ischemic Optic Neuropathy: Challenges for the Future

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Keywords: non-arteritic anterior ischemic optic neuropathy (NAION), neuroprotection, neuroregeneration, retinal ganglion cell (RGC), neuroinflammation

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INTRODUCTION

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common acute unilateral optic nerve (ON)-related cause of vision loss in people over age 50 (1, 2). However, despite the frequency with which this condition occurs, there is no treatment proven to improve vision in patients affected by NAION. Patient evaluation initially focuses on the exclusion of mimickers, specifically arteritic anterior ischemic optic neuropathy secondary to giant cell arteritis, as well as optic neuritis in atypical cases. After confirmation of the NAION diagnosis, the focus shifts to the identification of modifiable risk factors, including hypertension, diabetes, hyperlipidemia (3), obstructive sleep apnea (4, 5), and phosphodiesterase-5 inhibitor use (6, 7). Optimizing treatment of modifiable risk factors may decrease the risk of developing a sequential NAION in the fellow eye.

The pathophysiology of NAION, while not fully elucidated, is thought to be secondary to decreased perfusion of the anterior ON from short posterior ciliary arteries, leading to the development of optic disc swelling and, eventually, a compartment syndrome (8). The cause of the decreased perfusion (eg, hypotension, microthrombosis, a combination of these, or something else entirely) has not been confirmed. Studies also suggest that the inflammatory response to the initial injury may play a role in the resultant neuronal damage and visual loss (9, 10). Therefore, various potential neuroprotective and neuroregenerative treatments for NAION have been (and continue to be) evaluated.

CLINICAL RESEARCH

Many potential agents and procedures have been clinically assessed in the treatment of NAION, but none have clearly shown benefit and there is no widely accepted treatment regimen.

Medical Treatments

In a small double-masked, placebo-controlled study, no improvement in visual function was demonstrated with phenytoin treatment (11).

Aspirin has not shown benefit for visual outcome in eyes affected by NAION (12). While data have been inconsistent for a role in risk reduction for second eye involvement (13–15), there is no convincing evidence that aspirin prevents future NAION (16). Aspirin may be appropriate for secondary prevention of cardiovascular events (17), but the role of aspirin in primary prevention of cardiovascular events, even in the setting of known vasculopathic risk factors (and/or a prior NAION), is less clear, and recent reports have shown an increase in major hemorrhage without any significant reduction in risk (18). Therefore, the routine use of aspirin in patients with NAION is not recommended.

Both retrospective and prospective studies have evaluated the use of brimonidine, hypothesized to have neuroprotective potential, in patients with NAION. Neither study demonstrated benefit (19, 20).

The use of oral steroids in NAION is controversial. Hayreh and Zimmerman reported on a cohort of 696 eyes with NAION, comparing those treated with oral steroids with those not treated. Notably, the patients themselves selected their treatment group, with no randomization, masking, or placebo control. Among eyes with initial visual acuity of 20/70 or worse, treated within two weeks of onset, visual acuity and kinetic visual fields (assessed subjectively) were more likely to improve in the steroid-treated group than in the group that received no treatment (21). However, other studies (including randomized controlled trials and a meta-analysis) have found no significant benefit from treatment with oral steroids but have shown an increased risk of steroid-related complications (22–25). Therefore, routine use of oral steroids for treatment of NAION is not recommended.

The use of erythropoietin (administered intravitreally or intravenously) to treat NAION also is controversial. One interventional case series reported visual improvement in 55% of eyes treated with intravitreal erythropoietin, with a trend toward initial improvement followed by a gradual decline in vision thereafter (26). There was no control group, but the authors argued that the rate of visual improvement was superior to the rate of 39.5% previously reported in the natural history of NAION (27). One prospective study evaluating treatment with intravenous erythropoietin showed no effect on visual outcomes (23), though another randomized trial with a shorter inclusion window (within five days of vision loss, rather than 14 days) reported that 55% of patients treated with erythropoietin (versus 34% treated with steroid and 31% receiving placebo) gained three or more Snellen lines at the six-month follow up when compared with baseline (28), raising the question of whether erythropoietin could be useful in patients who present soon after vision loss.

A recent randomized, controlled trial evaluating treatment with subcutaneous RPh201 (an extract of gum mastic with possible immunomodulatory and neuroprotective effects) in patients with chronic NAION also was disappointing.

Surgical/Procedural Treatments

The Ischemic Optic Neuropathy Decompression Trial reported that ON sheath fenestration was ineffective and might be harmful in NAION (27). Hyperbaric oxygen treatment has not shown convincing benefit in NAION (29). While intravitreal anti-vascular endothelial growth factor (VEGF) therapy, used widely for the treatment of ischemic conditions of the retina, initially was reported as a promising treatment for NAION (30), no benefit was demonstrated in a non-randomized controlled trial (31). Intravitreal administration of QPI-1007 (a small interference RNA designed to inhibit expression of caspase 2) (32) and G-CSF (33) also have not demonstrated benefit.

BASIC AND TRANSLATIONAL RESEARCH

While the lack of benefit demonstrated in recent clinical trials has been discouraging to patients and the physicians who treat them, progress is being made in the laboratory setting. Two models of NAION, a rodent and primate model (rNAION and pNAION, respectively), have been developed for research into the pathophysiology of the disease, as well as for preclinical treatment trials (34, 35). Both models use laser-induced reactive oxygen species to promote capillary vascular thrombosis without affecting larger vessels (10). The pathophysiology in rNAION and pNAION mirrors the clinical disorder in terms of optic disc edema, ON axon loss, isolated retinal ganglion cell (RGC) loss, and ON dysfunction (10). Further, similar to human NAION, rNAION expresses significant variability in its severity and expression across different subjects, despite consistency of the induction technique (36).

Neuroprotection

The development of the rNAION and pNAION models has facilitated the assessment of a number of potential neuroprotective interventions. Many of these interventions function by suppressing the inflammatory response following RGC injury. Prostaglandin J2 (PGJ_2), an anti-inflammatory prostaglandin synthesized following central nervous system ischemia, led to a reduction in clinical, electrophysiological, and histological damage when administered as a single intravitreal dose five hours after the induction of pNAION (37) and immediately after the induction of rNAION (38). Potentially synergistic combination therapies with PGJ_2 are being explored, though up to this point, none have demonstrated efficacy beyond that of PGJ_2 alone (39). Daily topical ocular delivery of trabodenoson, a selective adenosine A_1 agonist, was shown to reduce ON edema and preserve RGCs in rNAION, when compared with vehicle (40). Further, intravitreal injection of ciliary neurotrophic factor (CNTF) was shown to promote RGC survival when administered one day after rNAION induction (41). Recent work has also found E212, a Rho kinase (ROCK) inhibitor, to have a neuroprotective effect when injected intravitreally immediately following rNAION. E212 was shown to suppress neuroinflammation and oxidative stress, as demonstrated by increased superoxide dismutase activity and decreased reactive oxygen species formation, leading to RGC preservation when compared with vehicle-treated eyes (42). In addition to topical or intravitreal treatment, alternative drug delivery methods have also been

explored. Polyamidoamine dendrimer nanoparticles have been shown to selectively target ischemic ON lesions in both pNAION and rNAION, suggesting that nanoparticle-linked therapeutics may provide a targeted route for drug delivery directly to the affected tissue in the future (43).

Neuroregeneration

Published studies using NAION-specific animal models have primarily focused on neuroprotective interventions, with the goal of preventing RGC loss after injury. However, ON regeneration, with the goal of restoring vision following RGC death, is an alternative approach to the treatment of NAION and other optic neuropathies. In 2013, the National Eye Institute (NEI) Audacious Goals Initiative (AGI) in Regenerative Medicine established the goal "to restore vision through regeneration of neurons and neural connections in the eye and visual system", thus directing significant resources toward this aim (44). Replacement of RGCs holds strong potential for restoring vision loss due to optic neuropathy and has been studied primarily in reference to glaucoma. RGC transplantation to restore vision requires multiple complex steps, each with its own unique challenges, including establishing a source for the RGCs, delivering the RGCs, promoting their survival and correct localization within the retinal structure, forming dendritic connections within the retina and growing axons toward the ON and, ultimately, further posterior to synapse in the lateral geniculate nucleus in a retinotopic arrangement, and ensuring myelination of the axons (45). While a complete review of the research in this area is beyond the scope of this paper, we will briefly discuss some exciting research breakthroughs.

Human-derived RGCs have been produced from numerous lineages, thus allowing for further study of transplantation *in vivo* (45). Some studies have shown functional improvements following RGC transplantation, including light-evoked electrophysiological responses from donor RGCs (46) and documented improvements in visually guided behaviors in recipient animals (47). However, there are still many challenges, particularly with regard to low rates of RGC engraftment and survival following transplant (45). One substantial limitation to engraftment of RGCs from an intravitreal approach is the structural barrier of the internal limiting membrane (ILM) (48). However, recent work has shown that the use of proteolytic enzymes to disrupt of the ILM prior to transplant is associated with a profound increase in neurite ingrowth in the retina (49).

Additionally, recent work has demonstrated that both molecular signaling and the external application of electric fields can be used to direct the growth of RGC axons. One study showed that a combination of neural activation and elevation of the pro-cell growth pathway mammalian target of rapamycin (mTOR) led to RGC axons regenerating long distances and forming connections with their correct targets (50). Another group demonstrated that ectopic expression of the *Oct3*, *Sox2*, and *Klf4* genes (three of the Yamanaka factors that can trigger mature cells to revert to an immature state) in mouse RGCs restored youthful DNA methylation patterns, promoted axon regeneration after injury, and reversed vision loss in a mouse model of glaucoma (51). Additionally, the application of electric fields was shown to direct axon growth from RGCs toward the cathode (52). A combination of these approaches may be required to promote and direct long distance axonal growth (initially toward the ON in the retinal nerve fiber layer, then through the ON, optic chiasm, and optic tract, to ultimately synapse in the lateral geniculate nucleus, all while maintaining retinotopic organization) following transplantation of RGCs.

DISCUSSION

While recent clinical trials have not identified an effective NAION treatment, they have collected vast amounts of data from patients affected by NAION. Further analyses of these data likely will advance our understanding of the factors surrounding NAION and perhaps provide insight into the similarities (and differences) between NAION in humans and experimental NAION in the animal models with which we work, thus clarifying the ways in which we interpret our laboratory results.

Regarding potentially neuroprotective treatments in the setting recent NAION, one key remaining challenge is to identify treatments that are effective within a clinically relevant treatment window, as most patients affected by NAION present days to weeks after the onset of vision loss, rather than within hours. Therefore, a treatment for which clinical trial recruitment would be feasible, and that could be anticipated to provide benefit in clinical trials and beyond, would need to be effective within this longer time window, rather than only when administered before or immediately following the onset of NAION. It is possible, and perhaps probable, that this may require combination therapies to address different inflammatory mediators at different time points after the acute ON injury. Studies in this area are ongoing.

Regarding RGC transplantation and ON regeneration, while exciting progress is being made on the various aspects of this approach, much work remains to develop a process to make this treatment a reality for our patients. Significant progress has been made in this area since the establishment of the NEI's Audacious Goal. Collaboration between teams of vision scientists working on the different steps of this process will continue to be of utmost importance moving forward.

Both neuroprotective and neuroregenerative approaches hold promise to provide treatments for our patients with currently untreatable NAION, as well as other optic neuropathies. Until treatments become available, clinicians must continue to focus on risk factor identification and management in patients with NAION.

AUTHOR CONTRIBUTIONS

AH contributed to conception and design of the work. AG and AH contributed to the data acquisition. AG and AH each drafted initial sections of the paper. All authors contributed to manuscript revision and approved the submitted version.

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REVIEW
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Giant Cell Arteritis: Updates and Controversies

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Abstract: Giant cell arteritis (GCA) is a systemic granulomatous vasculitis affecting the medium and large-size arteries, and may present with a range of ophthalmic findings. This review will cover GCA epidemiology, pathophysiology, clinical presentation, diagnostic workup, and treatment.

Epidemiology and Pathophysiology: GCA is commonly found in elderly patients and individuals of Scandinavian descent. Recent publications suggest it may be more common in African Americans and Hispanics than previously thought. It is very rare in Asian and Middle-Eastern populations, and there is little data regarding African populations. Genetic studies have identified increased risk associated with HLA-DRB1*04. Rather than a response to a specific antigen such as varicella zoster virus, current immunology research suggests that GCA results from changes associated with the aging immune system.

Clinical presentation to Ophthalmology: Arteritic anterior ischemic optic neuropathy is the most common ophthalmic manifestation of GCA, but central or branch retinal artery occlusion, ophthalmic artery occlusion, cranial neuropathies causing diplopia, and more rarely anterior segment ischemia and anisocoria may also occur. Clinical testing including visual field testing, OCT, OCT-A, ICG and fluorescein angiography can be helpful in suggesting a diagnosis in addition to the clinical exam.

Diagnostic Workup: GCA is ultimately a clinical diagnosis, but it is usually supported with lab results, pathology, and/or imaging. Temporal artery biopsy (TAB) remains the gold standard diagnostic test although its sensitivity is debated and practice patterns still vary with respect to sample length and whether unilateral or simultaneous bilateral biopsies are performed. Some studies have reported higher sensitivity of ultrasounds over TAB, with added benefits of time efficiency and cost effectiveness, promoting the diagnostic use of ultrasounds. MRI and even PET CT protocols offer additional options for less invasive diagnostic testing.

Treatment: Vision-threatening GCA is treated acutely with emergent admission for intravenous methylprednisolone, and long-term high dose oral corticosteroids remain the standard of care, despite common and sometimes serious side effects. The use of steroid-sparing alternatives such as tocilizumab is becoming more common and additional agents are being investigated.

Keywords: giant cell arteritis (GCA), MRI black blood, arteritic anterior ischemic optic neuropathy (AAION), epidemiology, vasculitis, temporal artery biopsy

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INTRODUCTION

Giant cell arteritis (GCA) is a systemic granulomatous vasculitis that affects medium and large arteries in patients over the age of 50 (1). GCA commonly presents with non-specific constitutional symptoms including fever, night sweats, anorexia, weight loss, fatigue, or myalgia. About half of patients diagnosed with GCA have polymyalgia rheumatica (PMR), a relatively common rheumatic disease of the elderly that presents with cervical, shoulder, and hip pain and stiffness (2). PMR and GCA share similar epidemiology and are both typically managed with glucocorticoids. GCA is classically distinguished by cranial ischemia-related symptoms such as headache, jaw claudication, and scalp tenderness, although large-vessel involvement leading to complications such as aortic aneurysm is becoming more widely recognized (3). This "extracranial" or "large-vessel" form of GCA can be more challenging to diagnose and to distinguish from PMR. Advances in diagnostic imaging as well as immunology are shedding new light on this form of GCA, and can also be helpful in the classic ("cranial") form of GCA. The classic cranial presentation of GCA is frequently associated with ophthalmic manifestations.

GCA poses a significant disease burden due to its potential risk of permanent visual loss, as well as frequent adverse side effects from long-term glucocorticoid treatment. One systematic literature review predicted that by 2050, more than 3 million people will be diagnosed with GCA due to the aging population, leading to visual impairment in 500,000 individuals in Europe, North America, and Oceania (4). In the United States alone, the projected cost from visual impairment due to GCA will exceed US$76 billion by 2050 (4). Prompt diagnosis and management of this disease may help reduce the burden of visual impairment. New research has challenged our understanding of the epidemiology, diagnosis, and treatment of GCA, and will hopefully promote better recognition, management and outcomes for patients.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Most epidemiological studies support relatively higher incidence rates of GCA in white populations, especially those of Scandinavian descent, with increased risk in women and individuals over 50 years of age (5). Incidence rates of GCA have been shown to vary amongst different European countries, with generally higher incidence rates in Northern European countries (**Table 1**). It has traditionally been understood that GCA is rare in non-white patient populations. However, most epidemiological studies of GCA have generally consisted of predominantly white populations in Europe and North America, and data regarding GCA incidence in other races and ethnicities remain limited. One study from Japan estimated a prevalence of 1.47 per 100,000 over age 50 (18) (for comparison, prevalence in Minnesota is 204 per 100,000 over 50 whereas incidence is 19.8 per 100,000 over 50), but other studies from Asia, Africa, and the Middle East are generally limited to case reports or retrospective reviews from single institutions (19, 20). For example, a study from the UK found 1 of 26 positive biopsies over 8 years was from a South Asian patient (21); another study from Mumbai found 21 patients over 15 years (22). Studies from a large center in Saudi Arabia imply a low incidence of GCA in the Arab population based on low rate of positive TAB (7/102 biopsies over 22 years) (23), and a low rate of arteritic anterior ischemic optic neuropathy (AAION) compared to nonarteritic anterior ischemic optic neuropathy (NAION) (24).

Given the ethnic and racial diversity in North America, estimates based on racial and ethnic groups within the United States have been used to compare populations: for example, a retrospective study of GCA from San Francisco reported the incidence of GCA in Asians was about 20 times less than in white patients (25). Interestingly, the evidence for GCA in the African American population has shifted over the years. An oft-cited study assessing the incidence of GCA in Shelby County, Tennessee from 1971-1980 reported the incidence of GCA to be 7 times greater in white patients compared to black patients (15). In contrast, another retrospective study conducted from the southern United States from 1974-1984 reported 13 out of 27 cases of GCA to be in black women (26). A larger study comparing the incidence of GCA in black and white patients in Baltimore from 2007-2017 supports the idea of GCA being more common than previously thought in black populations (or at least African Americans), with an estimated incidence of 3.1 per 100,000 over age 50 for black patients and 3.6 per 100,000 over age 50 for white patients (16). A recent multicenter study evaluated differences in presenting symptoms of GCA between 32 African American patients and 84 Caucasian patients with biopsy-proven GCA, and found that African American patients had significantly higher rates of headache, neck pain, anemia, and eye pain, and lower rates of jaw claudication and acute vision loss (27). To what extent these incidence estimates and clinical features can be extrapolated to African black populations is unknown, as the African American genome contains variable amounts of European (and other) genetic markers.

The incidence of GCA in Hispanic patients also remains a point of controversy. The first study in the US to evaluate GCA in Hispanic patients was a small retrospective study from Los Angeles which found that none of the 40 self-identified "Latino" Hispanic patients had positive temporal artery biopsy (TAB) results, compared to 19 of the 66 white patients—in this study patients were categorized as Hispanic or white, but not both (28). More recently, a study from Miami reviewed TAB results from 1996-2002 (29), distinguishing race and Hispanic ethnicity as two separate concepts, and reported similar prevalence and clinical course of GCA among Hispanic and non-Hispanic patients. It must be noted, however, that all of the patients with positive TAB identified their race as white. This difference in definition highlights the confounding problem that "Hispanic" reflects a diverse range of different racial groups and genetic heritages, just as race labels such as black, white, and Asian reflect a wide diversity of backgrounds, and individual patients may belong to multiple categories. If white generally

TABLE 1 | Incidence of GCA in various populations.

Country	Reported Race/Ethnicity	Criteria for GCA diagnosis	Incidence per 100,000 (over the age of 50)	Reference
Denmark	*	Clinical and pathologic diagnosis	20.4	Elling et al. (6)
France	*	Typical signs and symptoms	9.4	Barrier et al. (7)
Iceland	*	1990 ACR Classification Criteria, TAB, and clinical diagnosis	27	Baldursson et al. (8)
Italy	*	Positive TAB	5.8	Catanoso et al. (9)
New Zealand	*	Positive TAB	12.7	Abdul-Rachman et al. (10)
Norway	*	1990 ACR Classification Criteria, TAB, and imaging	16.8	Anderson et al. (11)
Spain	*	Clinical and pathologic diagnosis	10.13	Gonzalez-Gay et al. (12)
Spain	*	1990 ACR Classification, TAB, clinical diagnosis	2.2	Romero-Gómez et al. (13)
United Kingdom	*	Typical signs and symptoms	2.2	Smeeth et al. (14)
USA	African American	Clinical and pathologic diagnosis	0.36	Smith et al. (15)
USA	African American	Positive TAB	3.1	Gruener et al. (16)
USA	Olmsted County (population primarily of Northern European descent)	1990 ACR Classification, TAB, clinical diagnosis, and imaging	19.8	Chandran et al. (17)

**No specific racial/ethnic categories were reported.*

GCA, Giant cell arteritis; TAB, Temporal artery biopsy; ACR, American College of Rheumatology.

consists of those with European ancestry, it still does not capture the ten-fold differences in GCA incidence between different European populations, which have been well characterized.

Genetic and environmental influences have also been studied. The most consistent genetic association has been with HLA-DRB1*04 (30), but several other genes associated with cytokines, the innate immune system, and endothelial cells have been suggested to also have some influence, and there are also reports of familial GCA although this is rare (30, 31). Among environmental factors, seasonality and exposure to specific pathogens have been explored. Some studies suggest a seasonal variation with higher incidences of GCA in the summer months in Eastern Denmark (32), California (33), Southern Australia (34), and the UK (14). Other studies have reported higher incidence of GCA during the autumn and winter (35). Meanwhile, some other studies reported no significant correlation between GCA incidence and seasons (36, 37). Discrepancies in the results of these seasonal studies may be attributed to differences in the way the studies defined GCA (e.g. biopsy-proven or clinical diagnosis) or the definition of GCA disease onset (32).

Exposure to certain antigens has also been hypothesized to trigger GCA. In 2016 Gilden and Nagel proposed that varicella zoster virus (VZV) was a likely trigger, and they reported viral particles were found in TAB specimens, however most subsequent studies have found no relation between VZV exposure or VZV vaccination and GCA and many have failed to replicate the findings of VZV in TAB specimens, suggesting that the original finding may have been an artifact (38–40). Various other specific pathogens have been investigated, but it is more likely that at the population level there is some association with a wide range of preceding infections more generally, and not any one specific infectious agent (41).

Current understanding of the immunopathology of GCA implicates age-related dysfunction of the immune system and its interactions with the aging blood vessel wall rather than an immune response to any one specific antigen (31). When there is a constellation of genetic risk factors and environmental triggers, dendritic cells in the adventitia recruit T cells which leads to cytokine production, interferon gamma production, and inflammation including macrophages which can differentiate into giant cells (42). This inflammation remodels the vessel wall, leading to ischemia of the downstream organs. Proteins released by macrophages are being investigated as potential diagnostic and/or prognostic biomarkers that may be more specific than the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels (43).

CLINICAL PRESENTATION TO OPHTHALMOLOGY

The general clinical presentation of GCA is infamously variable; classic temporal arteritis—the "cranial" phenotype–is the one most associated with ophthalmic symptoms, but up to 20% of patients may present to the ophthalmologist with "occult" GCA—vision loss but no classic systemic symptoms (44). The rate of ocular involvement ranges from 10-70% in various studies (44, 45). GCA is well known in ophthalmology for its risk of irreversible blindness due to arteritic anterior ischemic optic neuropathy (AAION), which has been reported in over 80% of patients who present with ocular involvement (3, 46). Transient visual symptoms such as amaurosis fugax may often precede permanent visual loss (44). As shown in Mahr et al, ophthalmologists were the second most common referring specialty (after primary care), highlighting the

importance of ophthalmic symptoms in raising the suspicion for GCA (47).

AAION is characterized by ischemia of the posterior ciliary arteries (PCA) and loss of blood supply to the optic nerve head, with the medial branch of the PCA often affected (46). In the acute phase, AAION classically presents with severe vision loss (no light perception in up to 19% (48), and a swollen and chalky-white optic disc (**Figure 1**], progressing to optic atrophy within 6 to 8 weeks (**Figure 2**] (50). Patients with GCA may also present with arteritic posterior ischemic optic neuropathy (PION), which is less common and not visible on ophthalmoscopy (50). Up to 16% of patients with vision loss from GCA may have ischemic stroke (51), most often involving the vertebrobasilar territory (52). More rarely, cerebral ischemic lesions may result in visual loss (19).

GCA may involve occlusion of the central retinal artery (CRAO) in up to 14% of patients, or it may occlude the cilioretinal artery or other branches (46). Cotton wool spots may be seen in up to 30% of GCA patients who suffer early vision loss (46). Anterior segment ischemia and anisocoria are rare manifestations of GCA and may present with ocular hypotony, corneal edema, iris ischemia, and pupillary abnormalities (44). Ischemia of cranial nerves III, IV, and VI may result in diplopia, which can occur in up to 6% of patients, and more rarely ischemia of cranial nerve VII can present with eyelid position changes (51).

Visual field testing may be helpful in demonstrating the severity of visual field loss in ischemic optic neuropathy if the visual acuity is sufficient (e.g. 20/200 or better); typical AAION generally causes severe loss of visual field but a wide variety of patterns may be seen (51, 53). Visual field testing is helpful in identifying scotomas that the patient may not have noticed, for example, in the better seeing eye which may still have early ischemia. Fundus fluorescein angiography (FFA) or indocyanine green angiography (ICG) may exhibit significantly delayed filling of the choroid in patients with AAION (54). One study using FFA reported an average choroidal filling time of 69 seconds for patients with AAION, compared to an average of 5.8 seconds in normal subjects, or 5.5 seconds in nonarteritic AION (55).

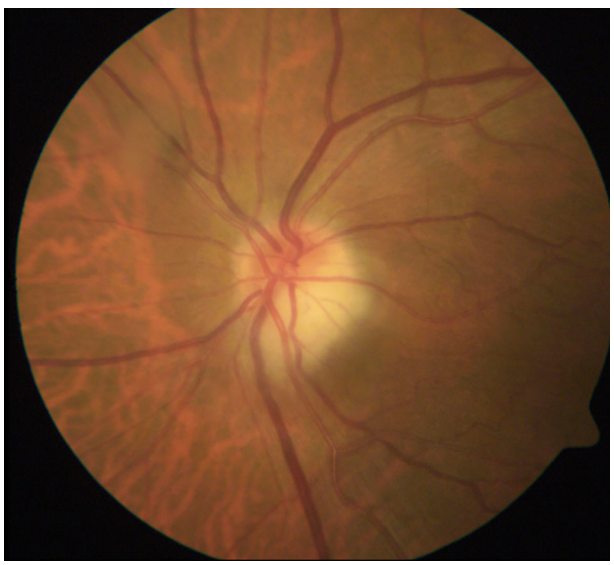

FIGURE 1 | Acute AAION. Image courtesy of Kimberly Gokoffski, MD PhD.

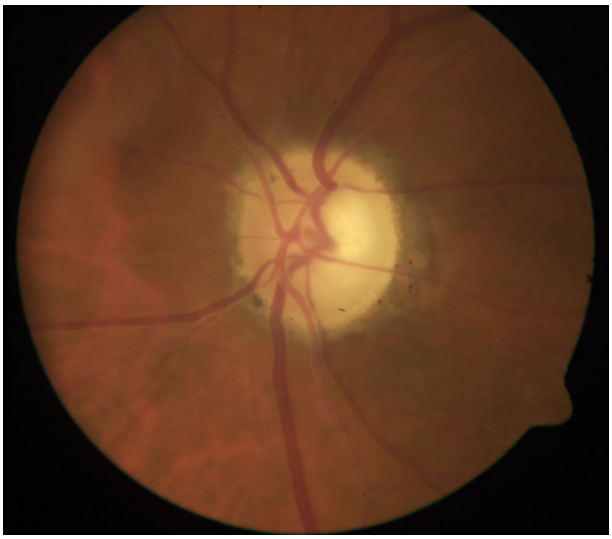

FIGURE 2 | Optic atrophy with apparent cupping after resolution of acute AAION. The optic disc atrophy following AAION (but not NAION) may resemble severe glaucomatous cupping. The remaining rim is usually pale after AAION but pink in glaucoma. OCT has been studied as a way to differentiate between glaucoma and atrophy after AAION: one study showed that non-glaucomatous cupping exhibited lower mean retinal nerve fiber layer (RNFL) thickness in the nasal quadrant, lower average macular thickness, and lower macular volume (49). Image courtesy of Kimberly Gokoffski, MD PhD.

Optical coherence tomography angiography (OCT-A), a non-invasive alternative to FFA and ICG, has also been shown to identify ischemic areas on the optic nerve head and reduction in vessel densities in patients with AAION (56). OCT-A may be more sensitive than FFA in its ability to visualize macular and radial peripapillary capillaries, but is not able to distinguish between AAION and non-arteritic anterior ischemic optic neuropathy (NAION) as well as FFA (56). A small case series suggested that changes in superficial microvasculature on OCT-A were not visible on FFA, although areas of choroidal hypoperfusion noted on FFA were not visible on deep laminar OCT-A segmentation (57). New advances on the horizon include laser speckle flowgraphy, which may improve our ability to distinguish acute AAION from NAION (58).

DIAGNOSTIC WORKUP

The diagnosis of GCA is a clinical one, supported by lab results, pathology, and imaging. The ACR classification criteria for GCA have often been used for diagnosis although they were intended for research studies (59). Up to a quarter of GCA patients may

have normal ESR, and C-reactive protein (CRP) may be a better inflammatory marker for clinical monitoring (3). Temporal artery biopsy (TAB) has traditionally been used for diagnosis but its sensitivity varies widely, and practice patterns vary over how and when to perform the biopsy and how to interpret the histopathology. Increasingly, ultrasound, MRI, and even PET CT are being used to evaluate for GCA (58).

Temporal artery biopsy (TAB) has conventionally been the gold standard for diagnosis, yet there are limitations pertaining to its low sensitivity and false-negative results. It is overall a very safe procedure, but potential risks include scalp necrosis, hematoma, infection, facial nerve damage, and rarely, cerebral ischemia (60). Clinical exam of the arteries is normal in about a third of positive TAB's, and the presence of localizing symptoms on one side does not necessarily mean the biopsy will be positive on that side (3, 61). The range of sensitivity for TAB has varied widely across studies, from 24-94%, possibly depending on factors such as length and processing of specimens as well as timing of biopsy after initiation of steroid therapy (3, 62).

To improve the sensitivity, some studies have advocated for longer arterial specimens, and/or simultaneous bilateral specimens, as well as protocols for pathologic sectioning to more adequately sample the entire length of artery and reduce the chances of missing skip lesions (63, 64).

More recent studies have argued that shorter specimen lengths are sufficient, with post-fixation length as low as 0.5cm although most authors recommend at least 1cm (which may correspond to almost 2cm pre-fixation) (62, 65). Studies of discordance have suggested rates of 3-9%, and surgeons continue to vary in whether they perform initial bilateral or unilateral biopsy (61). The American College of Rheumatology (ACR) recommends an initial unilateral temporal artery biopsy (TAB) of >1 cm within 2 weeks of starting oral (58). Current recommendations from both the British Society for Rheumatology (BSR) and European League Against Rheumatism (EULAR) suggest >1 cm biopsies corresponding to a post-fixation length of at least 0.7 cm, and do not routinely recommend taking a biopsy of the contralateral artery (66, 67).

Most studies agree, at least, that the specificity of TAB is quite high, although there are controversies regarding pathologic findings, particularly related to the concept of "healed arteritis" which can be difficult to distinguish from other age-related vascular changes (68). Classic findings of GCA on biopsy include, but are not limited to, histiocytes, epithelioid, and multinucleated giant cells between the intima and media, transmural inflammation marked by lymphocytic infiltrates, fragmentation of the internal elastic lamina, and intimal hyperplasia (62). However, multinucleated giant cells are only seen in about half of all positive specimens (3). Some studies have also used CD68, a marker for transmembrane glycoproteins on monocytes and tissue macrophages, in determining if a TAB is positive in the absence of multinucleated giant cells (69). Pathologists may also have discordant opinions on assessing histological features, as one study reported an intraclass correlation coefficient of 0.62 for TAB diagnosis (95% CI 0.49-0.76) (40). "Healed" arteritis is another controversial topic that is still not completely understood, where the biopsy is not normal but does not have active disease, and these may reflect a heterogeneous group of patients (68, 70). Furthermore, some have questioned whether TAB results actually change management—one studied reported that 87% of TAB negative patients remained on therapy due to clinical judgement (71).

Perhaps the most important factor for improving sensitivity in TAB (and other diagnostic testing) is pretest probability. Risk stratifying algorithms have been developed (72, 73), some are used in fast-track clinics to improve diagnostic accuracy and the sensitivity of screening ultrasound (73, 74). Because of the high incidence of false negative TAB, it has low negative predictive value, and various imaging modalities have been increasingly used to support (or exclude) the diagnosis of GCA. Imaging techniques such as temporal artery ultrasound (TAUS), which also include axillary arteries and color doppler imaging, have become first-line diagnostic tests instead of TAB in the 2018 European League Against Rheumatism (EULAR) recommendations (67). Positive ultrasounds in GCA present with a "halo sign" of dark hypoechoic area around the area of mural edema in the vascular wall (75).

A meta-analysis of 8 studies (605 patients) showed TAUS had sensitivity of 77% and specificity of 96% compared to clinical diagnosis (76). Standardized protocols for TAUS delineated by the TABUL study have been widely used in the UK and Europe (40, 46) but not in the United States (58). The main limitation regarding ultrasound is that it is highly operator-dependent: in the TABUL study, for example, the intraclass correlation coefficient for agreement was 0.61 among sonographers, although it should also be noted that the correlation coefficient was 0.62 among pathologists for TAB in that study (see also **Table 2**; 58, 62). Due to its non-invasive nature, ultrasound examinations provide the added benefit of examining the full length of both temporal arteries as well as the axillary arteries, offering greater sensitivity possibly due to longer persistence of abnormalities in larger vessels compared to temporal arteries (62). Furthermore, TAUS has been found to be cost effective relative to TAB (83).

Magnetic resonance imaging (MRI) can also be used in the diagnosis of GCA—findings include mural edema in the temporal arteries, as well as the ability to visualize other arteries (84). A meta-analysis of 6 studies estimated sensitivity of 73% and specificity of 88% for MRI compared to clinical diagnosis (76), suggesting that MRI is comparable to TAB in diagnostic value, and may spare TAB in patients with normal MRI findings. Furthermore, MRI is much less operator dependent compared to ultrasound (62). Potential drawbacks of MRI include limited availability and cost, as well as the limited detection of mural inflammation once steroid therapy has started (85), although more targeted protocols may allow for faster scan times and potentially reduced costs. MRA or CTA has also recently been recommended for all new GCA diagnosis given the high rate of aortic involvement (45, 86).

"Black-blood" is an MRI vessel wall imaging technique that creates high-contrast images of blood vessel walls that can be particularly useful for diagnosis of GCA. One study evaluating the diagnostic use of fat-suppressed 3D T1-weighted black-blood MRI within 48 hours of steroid initiation reported clear visualization of arterial walls and identification of mural

TABLE 2 | Diagnostic Testing for GCA.

Diagnostic Method	Sensitivity	Specificity	Intra-observer Correlation	Reference
TAB	39%	100%	0.62	Luqmani et al. (62)
TAB	61%	98%	Not reported	Dua et al. (77)
TAB	69%	100%	Not reported	Hansen et al. (78)
Ultrasound	77%	96%	0.61	Luqmani et al. (62)
Ultrasound	63%	79%	Not reported	Hansen et al. (78)
MRI	78.4%	90.4%	0.676	Klink et al. (79)
MRI with "black-blood" protocol	80%	100%	0.83	Rodriguez-Régent et al. (80)
FDG PET/ CT	71%	91%	0.65	Sammel et al. (81)
FDG PET/ CT	85%	83%	0.84	Grayson et al. (82)

TAB, Temporal artery biopsy; MRI, Magnetic resonance imaging; FDG PET, 18F-Fluorodeoxyglucose positron emission tomography; CT, computed tomography.

enhancement in GCA patients (80). Images were evaluated by 2 neuroradiologists and compared to clinical diagnoses of GCA, resulting in a sensitivity of 80%, specificity of 100%, and an inter-observer agreement of 0.83. Another study assessed the diagnostic use of MRI black-blood for detecting posterior ciliary artery (PCA) involvement in patients with GCA and AAION (87). 13 out of 18 GCA patients showed positive findings for AAION with MRI, with MRI black-blood findings displaying contrast enhancement around the optic nerve and adjacent orbital fat along the course of PCAs (87). Bilateral involvement of AAION was apparent in 12 out of 13 MRI black-blood cases, compared to only 6 out of 13 cases identified by ophthalmoscopy (87). These studies suggest that MRI black-blood may supersede ultrasound in its capacity for clearer readings and higher inter-observer agreement, and may be able to detect early ischemia even before profound vision loss occurs. Most centers with 3T MRI machines are able to perform black blood protocols and one should discuss with the radiologist to ensure the proper sequences are obtained.

18F-Fluorodeoxyglucose positron emission tomography (FDG PET)/computed tomography (CT) can be used to detect large-vessel vasculitis in the aorta and the subclavian, carotid, iliac, and femoral arteries, but has generally not been recommended as first-line for the assessment of cranial arteries (88). FDG PET/CT offers advantages in its ability to visualize all inflamed vessels in the body, as long as they are big enough to be detected. Potential drawbacks of using FDG PET/CT include its higher cost, the substantial amount of patient preparation, and exposure to ionizing radiation (88). Spatial resolution has improved with newer "time-of-flight" scanners such that PET/CT can reliably detect changes in cranial vessels (89), and recent studies have shown better results when scans are done within 72 hours of glucocorticoid treatment (81). One recent prospective study using time-of-flight PET/CT within 72 hours of glucocorticoid treatment revealed a sensitivity of 71% and specificity of 91% when using clinical diagnosis as the standard, with interobserver reliability of 0.65 (81).

TREATMENT

High-dose glucocorticoids have been the mainstay in treating acute GCA. The 2018 EULAR recommendations suggest 40-60 mg/day prednisone equivalent in treating acute GCA, 15-20 mg/day within 2-3 months, and ≤5 mg/day after 1 year to avoid relapse (67). In emergent situations where GCA patients present with acute visual loss or amaurosis fugax, high dose (up to 1 g/day) intravenous methylprednisolone is recommended for up to 3 days, then transitioning to 1 mg/kg oral prednisone (67). Specialized centers for diagnostic work-up within 24 hours of presenting symptoms of GCA, called "fast-track clinics" in Norway and the UK, have been shown to reduce the risk of permanent visual loss, highlighting the importance of rapid diagnosis and treatment of GCA (90, 91). Overall, there has been a decrease in permanent blindness associated with GCA over the past several decades, likely due to earlier recognition and treatment (48).

Because of the high incidence of visual symptoms, ophthalmologists play a key role in the early/acute treatment of GCA. Rheumatologists generally manage the long-term steroid dosing or steroid-sparing agents. The effectiveness of corticosteroid therapy is often monitored by measuring ESR and CRP over time (44), but these inflammatory markers may not consistently reflect disease activity (75). Patients usually require at least 2 years of corticosteroid therapy, and most are able to taper off by 5 years after diagnosis, but relapse of GCA is common when glucocorticoids are tapered (92). While there is no major consensus on treatment regimens for relapse, the EULAR recommendations suggest treating "major relapse", defined by clinical symptoms of jaw claudication, visual symptoms, visual loss, scalp necrosis, stroke, limb claudication, or active aortic inflammation, with high dose glucocorticoids of 40-60 mg/day (67). Minor relapses, defined by recurrence of active disease without fulfilling the criteria for a major relapse, are recommended to be treated 5-15 mg above the last effective dose of glucocorticoids.

Long-term treatment with high-dose corticosteroids carries high risk of complications, including but not limited to osteoporosis, diabetes, cardiovascular disease, and glaucoma. In light of these potential complications, the role of glucocorticoid-sparing agents are being studied in the maintenance of GCA remission (51). Methotrexate (MTX) is an antifolate that interferes with DNA synthesis. It is widely available, affordable, and oral, but outcomes associated with MTX in treating GCA have been variable. A meta-analysis of 3 randomized placebo-controlled trials was performed showing that MTX reduced corticosteroid dose by 842 mg within 48 weeks, and had a higher probability of sustaining discontinuation of

corticosteroids for ≥24 weeks (93). However, further research is necessary in determining whether methotrexate has a clear benefit in the treatment of GCA.

Tocilizumab (TCZ), a humanized monoclonal antibody that blocks the interleukin-6 receptor, is given by subcutaneous injection every 1-2 weeks, and is the first FDA-approved therapy specific for GCA. Increased interleukin-6 (IL-6) levels are thought to induce acute phase response and systemic manifestations of GCA (94). Randomized controlled trials have shown that tocilizumab has significantly lower rates of relapse and lower exposure to glucocorticoids (60). A randomized placebo-controlled phase 3 clinical study called the Giant-Cell Arteritis Actemra (GiACTA) trial showed that 162 mg of tocilizumab weekly or every other week in combination with a prednisone taper over 26 weeks was superior in sustaining remission, compared to a placebo and prednisone taper over 26 weeks, or a placebo and prednisone taper over 52 weeks (95). Furthermore, adverse events were lower the in tocilizumab group (15% vs 22%) although the study duration was too short to potentially capture long-term side effects of glucocorticoids or tocilizumab (96). A recent paper of real-world use supported the efficacy of tocilizumab in sustaining remission, and specifically noted no new flares associated with vision loss once patients were started on tocilizumab (97).

There are additional targeted agents against IL-6/IL-6R as well as targeted therapies against T-cells which are being studied in GCA (abatacept and ustekinumab), suggesting that the treatment landscape may be quite different in a few years.

DISCUSSION

Giant cell arteritis is the most common form of vasculitis in adults, with frequent and often devastating ophthalmic manifestations (50). Recent advances in our understanding of GCA diagnosis and management hold the promise of better detection and better treatment outcomes for patients.

Recent epidemiologic studies have demonstrated that incidence rates of GCA in African American populations are higher than previously thought. Variation in the definition of Hispanic underlies the conflicting study results regarding GCA rates in that very heterogeneous population. The largest incidence studies come from European nations with nationalized healthcare systems that facilitate population level analysis. The increasing ability to explore big data in the United States whether through the Intelligent Research in Sight (IRIS) registry or insurance/Medicare databases may help gather more insights on GCA and related ophthalmic complications in more diverse populations.

The ophthalmologist often plays a key role in suspecting the diagnosis of GCA, and that is unlikely to change despite advances in technologies to support that diagnosis.

Once GCA is suspected, a thorough ophthalmic exam and testing including visual fields, OCT, OCT-A, FFA, and/or ICG can help support the diagnosis, and emerging technologies such as laser speckle flowgraphy are being studied. Noninvasive radiologic imaging such as TAUS, MRI, or PET may be used to confirm or exclude the diagnosis, evaluating the entire length of the temporal arteries on both sides, as well as other vessels. Algorithms for stratifying risk/pre-test probability can be applied to improve diagnosis. Advances in MR and PET protocols as well as deep learning algorithms for ultrasound interpretation will likely further improve the sensitivity, specificity, and clinical utility of these modalities. MR or CT imaging is also increasingly used to screen for aortic as well as cerebrovascular complications. TAB nevertheless remains the gold standard for many physicians to confirm a diagnosis of GCA; the majority of recent studies and guidelines suggest a post-fixation TAB length of 1cm is sufficient, especially if the pathologist samples extensively along the entire length of submitted artery.

Once the diagnosis is confirmed, long-term glucocorticoids remain the backbone of GCA therapy for now, but tocilizumab and other agents may be used to reduce overall glucocorticoid exposure and its associated complications, and additional new therapies are being investigated. Further studies on dosing and longterm adverse effects are needed, and advances in immunology may provide more useful biomarkers than ESR and CRP to diagnose and/or follow treatment effect. Collectively, these advances are changing the way we perceive and manage this common but challenging condition.

AUTHOR CONTRIBUTIONS

JC conceived the idea and scope of the review. EY and JC both performed literature review and wrote the manuscript. All authors agree to be accountable for the content of the work. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Cavernous Sinus Syndrome as the Initial Presentation of Multiple Myeloma

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Multiple myeloma (MM) is the second most common hematologic malignancy and most common primary bone malignancy. Ocular manifestations of MM are extremely rare and may be the first presentation leading to diagnosis. Ophthalmologists routinely encounter cavernous sinus syndrome, and there is a wide range of possible etiologies. Here, we present a case of a patient presenting with diplopia, ptosis, and ophthalmoplegia found to have a cavernous sinus plasmacytoma with systemic workup consistent with MM. MM is a rare cause of cavernous sinus syndrome and should be considered in the setting of a skull base mass.

Keywords: oncology, neuroophtalmology, cavernous sinus, cranial nerve (CN) disorders, multiple myeloma

INTRODUCTION

Multiple myeloma (MM) is a malignancy characterized by monoclonal proliferation of plasma cells in the bone marrow that can cause lytic lesions, frequent infections, and renal failure or can present asymptomatically (1). Plasmacytomas are malignant plasma cell neoplasms that can occur as solitary disease or as a feature of MM. Solitary plasmacytoma can present as extramedullary plasmacytoma (EMP) or solitary bone plasmacytoma (SBP). Plasmacytomas can also be secondary to MM when associated with systemic disease (2). SBP or EMP cannot be diagnosed without a systemic workup including bone marrow biopsy to rule out MM, and still up to 85% of those with solitary plasmacytoma will eventually develop MM (3).

Periocular involvement of MM is extremely rare, and only around 50 patient reports exist in the literature (4). When there is orbital involvement, the most common presentations are proptosis and periocular swelling, and the ophthalmoplegia or ptosis is more rare (5). Plasmacytoma of the cavernous sinus is even more rare, with only a few reports in the literature. We report a case of a 60-year-old man who presented with diplopia, ptosis, and ophthalmoplegia found to be due to a plasmacytoma of the cavernous sinus associated with concomitant MM.

CASE PRESENTATION

A 60-year-old man with a past medical history of diabetes and hypertension presented to the emergency room with intermittent diplopia and pain above his left eye for 2 weeks. He reported ptosis of the left eye for 1 week. On ophthalmic examination, he reported that the ptosis had been progressively worsening over the last week. Visual acuity was 20/20 in both eyes with normal intraocular pressure. Pupils were notable for left mydriasis, poor reactivity to light, without an afferent pupillary defect. Extraocular movements were notable for a −1 limitation on supraduction and infraduction of the left eye, without deficit on intorsion or external rotation. Sensation in the distribution of the trigeminal nerve was not checked at initial presentation. External exam was notable for ptosis with margin to reflex distance 1 (MRD1) of 2 mm and a mild exotropia of the left eye. Fundus exam was unremarkable.

A CT head revealed a 3.2 × 3.3cm left clival mass with cavernous sinus and sphenoid sinus extension and associated osseous erosion. An MRI was performed, which demonstrated a 3.5-cm enhancing destructive mass within the clivus extending into the left cavernous sinus and partially encasing the left cavernous internal carotid artery (**Figure 1**). Smaller enhancing lytic skull base lesions were also noted. The patient initially refused biopsy of the lesion and his clinical examination rapidly worsened. Four days after initial examination, he developed complete ptosis with a fixed and dilated pupil. His motility worsened with inability to supraduct, infraduct, and adduct and −3 abduction (**Figure 2**). He underwent repeat imaging with MRI brain and orbits, which did not show interval change in size of lesion. Endoscopic biopsy at that time of the mass involving the sphenoid sinus was consistent with lambda light-chain restricted plasmacytoma (**Figure 3**).

Systemic workup was performed with skeletal survey, demonstrating multiple lytic and destructive bone lesions throughout the pelvis, multiple vertebral bodies, and bilateral proximal femurs. Serum protein electrophoresis was notable for an M-spike of 3.8g, with an Immunoglobulin G (IgG) prevalence and elevated lambda light chains. Bone marrow biopsy was performed, which demonstrated >10% plasma cells, found to be IgG lambda light-chain restricted MM with high-risk cytogenetics, FGFR3-IGH gene rearrangement [t(4;14) translocation] (**Figure 3**).

He was started on pulse steroids with dexamethasone for 4 days and then received radiation therapy to the base of the skull at 3,500 cGy. He was discharged on a dexamethasone taper with plans to start systemic therapy. He was seen in our eye clinic 1 week after skull-based radiation therapy and, unfortunately, had no improvement in his clinical examination. The initiation of chemotherapy was delayed due to COVID-19 infection and subsequent failure to thrive. After recovery from COVID-19, the plan was to begin bortezomib; however, the patient developed hypercalcemia and altered mental status after the first dose. Imaging showed worsening lesions of the thoracic spine with cord compression. The decision was then made to stop chemotherapy and pursue palliative care measures. Unfortunately, the patient expired shortly thereafter, just 5 months after diagnosis.

DISCUSSION

MM is a systemic disease that is characterized by a monoclonal proliferation of plasma cells that are detectable in the serum or urine (6). It effects 7.1 per 100,000 men and women per year in the United States with a median age at diagnosis of 69 years old (7). With localized disease the 5-year survival rate is 77.5%; however, the 5-year survival rate drops to 54.5% when there is distant spread (7).

In a healthy individual, plasma cells are produced from B cells that produce immunoglobulins. Each immunoglobulin contains a heavy chain and two light chains. The five types of heavy chains

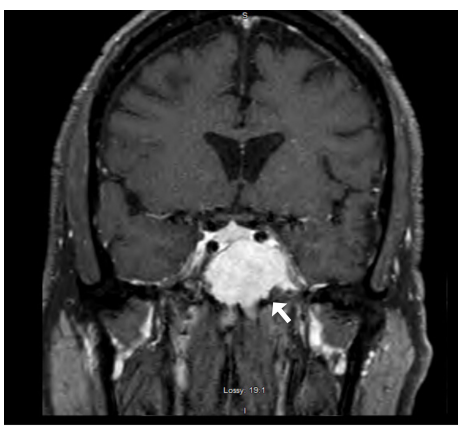

FIGURE 1 | T1-enhanced fat-suppressed coronal MRI demonstrating a large avidly enhancing mass involving skull base with the majority of tumor burden centered in clivus with invasion of left sphenoid sinus and left cavernous sinus.

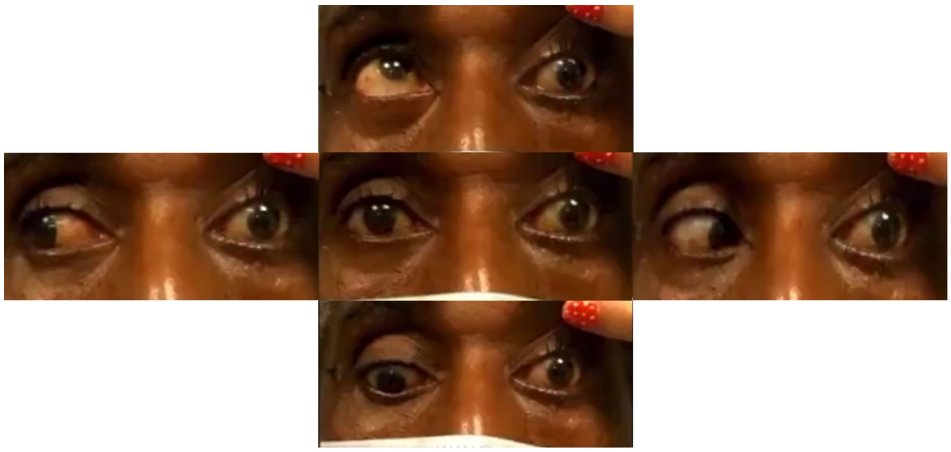

FIGURE 2 | Extraocular movements demonstrating reduced supraduction, infraduction, abduction, and adduction of the left eye with a down and out left eye in primary gaze (center).

are IgG, IgM, IgA, IgE, or IgD (8). Light chains can be kappa or lambda. Most commonly in MM, there is preponderance of IgM or IgG. As MM continues to progress, light chains will be produced at a greater rate than heavy chains, which can be useful in monitoring disease progression. Screening includes measuring serum and urine protein electrophoresis, immunofixation studies in serum and urine, and detection of immunoglobulin free light chains. In patients where serum and urine testing is suspicious for

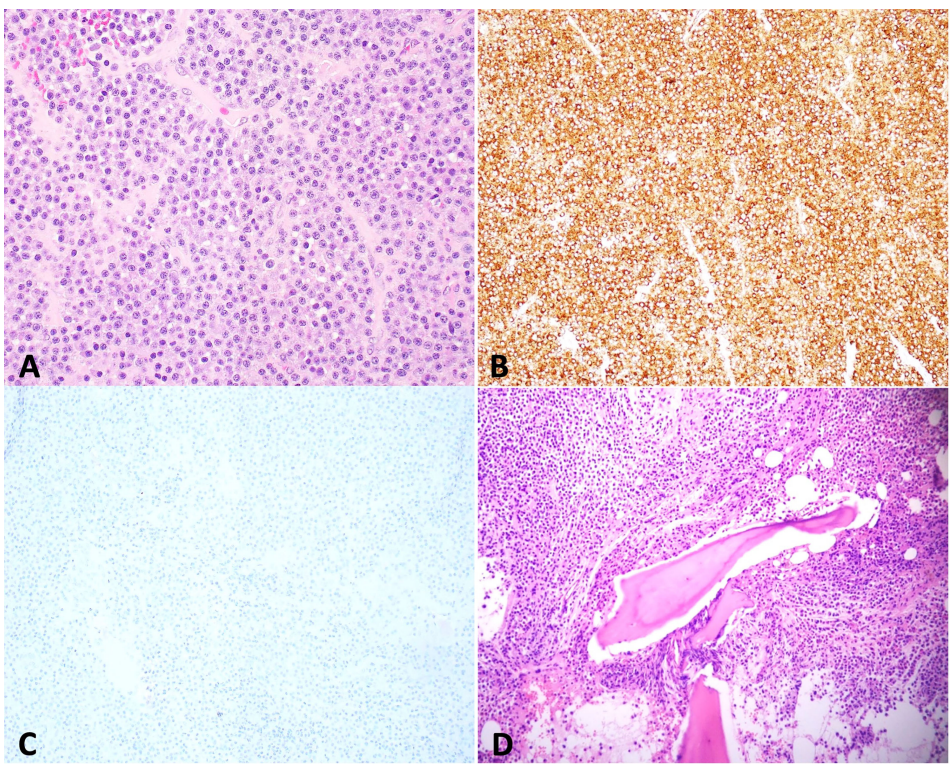

FIGURE 3 | Biopsy of skull base mass shows sheets of plasma cells [**(A)** hematoxylin and eosin stain (H&E), 400×] that are positive for lambda [**(B)** 100×] and negative for kappa [**(C)** 100×] by immunohistochemistry, indicating lambda light-chain restriction. Bone marrow biopsy reveals that sheets of plasma cells infiltrate in bone marrow [**(D)** H&E, 200×] with lambda light-chain restriction (date not shown).

myeloma, bone marrow biopsy should be performed. Diagnosis of MM requires at least 10% of plasma cells in the bone marrow or biopsy-proven bony or EMP, plus the presence of one myeloma defining event: hypercalcemia, renal insufficiency, anemia, or osteolytic bone lesions (9).

Plasmacytomas are histologically the same as MM, with tumors showing predominantly plasma cells that stain positively for CD38 and CD138 with the majority having immunoglobulin light-chain restriction (4). Plasmacytomas typically begin in the bone but can also found in soft tissue and are then designated extramedullary (2). SBP or solitary EMP has a better prognosis than MM alone; however, many will eventually develop MM (10).

In MM, the most common manifestations on presentation are anemia, infections, lytic bone lesions, or renal insufficency (6). Periocular involvement in MM is extremely rare and can be due to local tumor growth or hematologic abnormalities due to the underlying plasma myeloma and, therefore, can affect virtually any part of the eye. Intraocular manifestations that have been reported include uveal cysts, corneal crystals, exudative macular detachments, vascular occlusions from hyperviscosity syndrome, and retinal hemorrhages or cotton wool spots (11). Many of these findings, however, may be asymptomatic or found on autopsy (12). Orbital involvement of MM has also been reported. In a review, Burkat et al. found that, of 52 patients with orbital involvement, 35% of had orbital symptoms as their initial presentation of their disease (10).

Cavernous sinus involvement, however, is more rare and has been reported in only case reports and series (13–28). The majority of cases reported are in patients with known diagnoses of MM or EMP (15, 20, 21). Of these case reports, there were only three patients whom initially presented with cavernous sinus syndrome that eventually lead to a diagnosis of MM. Each of these three cases had varied clinical presentations. Ko et al. reported a 48-year old-male who presented with vertigo, diplopia, and intermittent left retro-orbital pain for 1 week and was found to have left abducens palsy with left V2 hypesthesia. The patient was initiated on corticosteroids before imaging was obtained for presumed Tolosa-Hunt Syndrome. Eventually, imaging and laboratory work confirmed a cavernous sinus mass and a diagnosis of MM. The mass was removed and histological examination confirmed plasmacytoma. Galea et al. reported a 58-year-old female patient who presented with vertical diplopia and variable left upper lid ptosis. Examination was notable for limitation of supraduction that worsened on left gaze. This patient was initiated on chemotherapy without mention of radiation to the skull base lesion. Last, Lam et al. reported a 76-year-old male patient who presented with diplopia and was found to have 1 mm of right ptosis, limitation of adduction, elevation, and depression of the right eye with right V1 hypesthesia. Imaging was nonconclusive without evidence of a mass. The patient was treated only with corticosteroids. Given the aggressive nature of the disease, the patient died 3 months after presentation. An autopsy revealed that the cavernous sinus was filled with malignant plasma cells. These patients presented similarly to the present case with varied cranial nerve involvement.

Cavernous sinus syndrome often presents with multiple cranial nerve palsies. Prompt imaging must be performed to rule out life-threatening diagnoses including tumor, aneurysms, or arteriovenous fistulas. Our case highlights the importance of histological examination of tumors involving the cavernous sinus when tissue can be safely taken, as the diagnosis of plasmacytoma lead to discovering systemic MM in this patient. In this case, the mass extended into the sphenoid sinus, providing a safer biopsy location. Plasmacytoma must be included in the differential diagnosis of any cavernous sinus mass, contributing to multiple cranial nerve palsies. These tumors can progress rapidly as in our patient who had worsening ophthalmoplegia and ptosis in just 4 days during admission. In a case reported by Lam et al., similarly. the patient's clinical exam worsened rapidly over 2 weeks even with steroid initiation (15). This potential for rapid decline has not been well documented and highlights the importance of prompt diagnosis and treatment. Treatment of plasmacytoma is typically with radiotherapy of the mass, with chemotherapy in conjunction for systemic myeloma. There have been reports suggesting that adjuvant chemotherapy should be considered even in solitary EMP (26). This is in contrast to other tumors of the clival region in which neurosurgical resection would be mandatory, highlighting again the importance of biopsy in plasmacytoma.

Our case highlights a rare presentation of MM. There have been very few reports in the literature demonstrating cranial nerve palsies as presenting clinical features of MM. Few of these reports have been in the ophthalmic literature. Plasmacytomas and MM can be asymptomatic until spread is more severe; therefore, it is important that ophthalmologists are aware of the way in which plasmacytomas can present in the orbit and periocular region. Plasmacytoma is important to consider on the differential diagnosis of any space occupying lesion involving the orbit and cavernous sinus. A multidisciplinary approach is of the upmost importance in ensuring appropriate and timely diagnosis and treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the relevant individual for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors contributed to manuscript writing and revision and read and approved the submitted version.

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OPINION
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Advocating Patient-Centred Research in Ocular Myasthenia Gravis (OMG): A Call for an OMG Research Consortium

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Keywords: myastenia gravis, patient–centred care, extraocular muscle, ocular myasthenia gravis (OMG), prognosis

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INTRODUCTION

Ocular symptoms in myasthenia gravis (MG) are common, affecting up to 85% of patients with this autoimmune neuromuscular junction disease (1, 2). MG can cause ocular symptoms of diplopia and ptosis, and generalised weakness of limb, bulbar or respiratory muscles. In patients with MG limited to ocular signs and symptoms only, i.e. Ocular Myasthenia Gravis (3, 4), there is a 30-80% risk of converting to Generalised Myasthenia Gravis (GMG) (1, 2, 5, 6).

Traditionally, OMG has been considered a milder version of MG, classified as Class I in the Myasthenia Gravis Foundation of America (MGFA) clinical classification where the consecutive numerical increase from Classes I to IV indicates worsening severity (7).

However, diplopia and ptosis can cause significant disability and impact quality of life (8, 9), which raises the question of whether OMG (MGFA Class I) is truly milder in its impact to patients, compared to mild limb weakness of GMG (MGFA Class II). Therefore, this opinion paper advocates that OMG is best considered a subgroup of MG (10), rather than the mildest subtype of MG, concurring with other researchers in this area (10).

This is also pertinent as there are unique considerations to OMG, some outlined below. These and more, would be research questions best served through concerted collaborations within an OMG research consortium – this paper is a call for such a collegial consortium.

OMG RATING SCALES AND PATIENT REPORTED OUTCOME MEASURES

MG rating scales focus on GMG symptoms and insufficient for monitoring people with OMG (11). To truly support patient-centred care, we need to fully understand the extent of disease impact on our patients (12). An extended ocular version of the Quantitative Myasthenia Gravis (ocular-QMG) rating scale showed promise as a tool for monitoring change of ocular symptoms, in a study demonstrating the effectiveness of steroids, although the ocular-QMG scale was not further

validated (13). The Ocular Myasthenia Gravis Rating Scale (the OMGRate) was developed to address this gap (14). The OMGRate comprises of two components: a clinical examination (OMGRate-e) and a patient questionnaire (OMGRate-q). Data from a single-centre of 104 patients (67 males, mean age 55 years, range 18-86), showed good external validity: the examination component of the rating scale, OMGRate-e, had good correlation with the MGC (r=0.64, 95% confidence intervals [CI] 0.54-0.74, p<.0001); good correlation between the OMGRate and MG-QOL15 (r=0.68, 95% CI 0.60-0.77, p<.0001). As the cohort studied was from a single centre, the next step is to validate the OMGRate in a multicentre study.

Alongside this, patient report outcome measures (PROMs) are also needed for patient-centred research, as PROMS measure the impact of disease and treatments without intervening interpretation from clinicians and researchers (15). For example, the degree of ocular deviation or measurement of ptosis is not as important to the patient, compared to the functional impact of this on their daily activities. The use of PROM in MG has been shown to be effective and facilitates delivery of tele-healthcare (16). The questionnaire portion of the OMGRate (the OMGRate-q) has shown good external validation and therefore potential to be validated as a standalone PROM for OMG (14). A high-quality PROM for OMG is critical for patient-centred research trials comparing OMG treatments, particularly with new therapies in the horizon (17).

MONITORING CARE IN CLINIC

An important aspect of care in OMG is to monitor for the development of GMG, including limb, bulbar and respiratory weakness. The respiratory function assessment in MG traditionally uses a spirometer to measure the forced vital capacity (FVC), and a reduction of FVC from standing to supine positions could indicate diaphragmatic weakness (18). Unfortunately, spirometry is aerosol generating, limiting its use since the COVID-19 pandemic. The single breath count (SBC) can be a surrogate measure of vital capacity in GMG (19), useful for screening for exacerbations of MG (20), and in OMG may show a decrease in SBC prior to onset of respiratory symptoms (21). An alternative, non-aerosol generating method of monitoring respiratory function test is the sniff nasal inspiratory pressure (SNIP) (22), although research to validate this in OMG is needed.

IMPROVING DIAGNOSTIC YIELD

One of the potential difficulties experienced by people with OMG, is the delay in diagnosis, particularly in seronegative patients who comprise 40-50% of all OMG (4, 5). Approximately 50% of people with OMG have antibodies against the acetylcholine receptor (AChR) (4, 5). A small number have the antibodies against the muscle specific kinase (MuSK) or the low-density lipoprotein receptor related protein 4 (LRP4) (4). The serological diagnostic yield can be improved with cell-based assays, where the clustered AChR receptor antibodies can be detected in up to 25% of seronegative OMG (23). Therefore, a proportion of patients are still seronegative, and concerted effort to discover antibodies in these patients will aid clinical diagnosis.

Neurophysiology with repetitive nerve stimulation have limited sensitivity in OMG (4). Single fibre electromyography (SFEMG) of frontalis or orbicularis oculi can improve the sensitivity rate, but can also be abnormal in other non-MG conditions (4, 17). SFEMG of EOM muscle has been reported (24), but not widely adopted. More recently, the ocular vestibular evoked myogenic potentials (oVEMP) have shown promise as a diagnostic tool in MG. In a study of 27 patients with MG (13 OMG, 14 GMG), oVEMP had an 89% sensitivity and 64% specificity for MG (25, 26). The oVEMP is a promising novel diagnostic tool and merits further research into its clinical utility, particularly in seronegative OMG where diagnosis is arguably more difficult.

WHY OCULAR MUSCLES ONLY? CLINICAL PHENOTYPING AND EXTRAOCULAR MUSCLES RESEARCH

An interesting unanswered question is why some patients with OMG have a predominantly 'ophthalmoplegic' phenotype with large ocular deviations, whereas others have minimal extraocular muscle weakness with significant variability in signs and symptoms. Clinical phenotyping of OMG by clinical examination and serology may provide further insights into its pathophysiology, particularly alongside the study of extraocular muscles (EOMs).

EOMs are unique and differ from skeletal muscles, possessing six different muscle fibre types, compared to four in skeletal muscles, of different size, contractile speeds, & fatigue resistance (27). The reasons for these differences are not fully understood, but likely due to the unique demands of eye movements for speed, endurance of static holds, & precision.

EOMs are susceptible in MG due to reduced folding of the postsynaptic membrane at the neuro- muscular junction (28), deficiency in complement inhibitory proteins (29), and a high physiological demand for sustained and precise ocular alignment (28). EOMs are also divided into global and the orbital layers (see **Figure 1**), with functional differences as reflected by different fibre types in these respective layers, e.g. in initiating eye movement versus gaze holding (27, 30–32). A hypothesis of interest to study in OMG, is whether the orbital and global layers are preferentially affected in the different OMG clinical phenotypes.

Gene expression studies are a promising area of research for OMG, as they can reveal functional differences in the EOM layers (33, 34). In contrast to anatomical studies which look at the morphology of the tissue, RNA expression can show differences in functions of cells of similar morphology, and can also elucidate effects of epigenetics or chromatin control in the way genes are expressed (35).

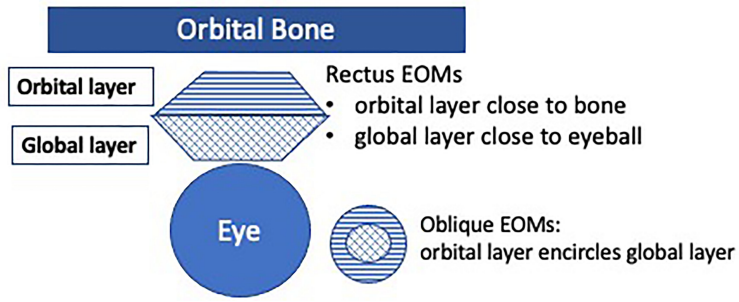

FIGURE 1 | The extraocular muscles (EOMs) are divided into two layers: the orbital and the global layers. The orbital layer initiates movement, and the global layer activates later. Orbital layers consist of 20% multiply innervated fibres (MIF), and 80% fast-twitch singly innervated fibres (SIF). Global layers consist of 10% slow-twitch MIF and 90% fast-twitch SIF (including red, intermediate and white muscle fibres) (27).

Oculography studies to objectively measure eye movements in OMG can shed further insight into its pathophysiology. Cogan and colleagues demonstrated that in MG with severe ophthalmoplegia, there was relative sparing of fast twitch fibres when tonic muscle fibres responsible for maintenance of eccentric gaze hold were severely affected (36). They also showed that in some MG patients, small amplitude saccades were hypermetric and had high velocities, appearing as twitch/quiver movements characteristic of MG (36, 37). Barton and Sharpe showed that saccades of MG patients had more variability in the initial and fatigue periods compared to those without MG, concluding that saccadic jitter may be a useful diagnostic sign in 42% of myasthenic saccadic analysis (38). Additionally, increased microsaccadic movements in OMG compared to healthy controls may suggest frequent 'recalibration' to maintain gaze hold (39).

Another promising area of research is the use of magnetic resonance imaging (MRI) to evaluate the EOM in MG. Recent research techniques showing fat replacement or atrophy in MG can help elucidate the disease pathophysiology (40, 41). Using these techniques as part of the clinical phenotyping of OMG can be illuminating.

THE RISK OF SECONDARY GENERALISED MYASTHENIA GRAVIS

Last but not least, the risk of SGMG is another important area for further research. The reported risk of SGMG has varied widely, ranging from 30-80% (1, 2, 5, 6). Whether the risk of SGMG can be modulated by immunosuppression or thymectomy remains controversial (5). To address this, a large randomised controlled trial of 304 newly diagnosed OMG will need to be recruited (42), and such an endeavour can only be achieved through a large multicentre study. However, the sample size needed may be less if we can selectively recruit patients at high risk of SGMG. Our earlier work has showed by proof-of-principle that a 'risk of generalization' (ROG) score can be created, allowing us to stratify patients into high or low risk of SGMG (42). This study was based on a retrospective cohort. Data analysis to further develop the ROG score with a prospective cohort is currently in progress (43).

There are a number of high-quality MG registries (44, 45), and work is also needed alongside this for an OMG registry with clinical phenotyping of OMG (43). Such a registry will prepare the groundwork for future treatment trials, supporting successful participant recruitment. Such registries will also support development of biomarker studies on predicting the risk of SGMG (46), and the search for antibodies in seronegative patients. Severity of OMG can be a risk for SGMG (47), and a multicentre OMG registry, that includes high quality PROM and rating scales, can support the ongoing development and refinement of a robust ROG score. A robust ROG score will also allow us to better counsel patients on their risk of SGMG, as part of delivering patient-centred care.

CONCLUSIONS

With rare conditions such as OMG where research funding is relatively limited, a concerted, cohesive and collaborative effort is the way forward, for the benefit of patients who are most affected by this condition. An OMG research consortium that pulls together researchers in the field and our respective strengths and expertise, will benefit patients, enable high quality patient-centred research that translates to patient-centred care.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Apraclonidine—An eye opener

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Pharmacological testing with apraclonidine eye drops induces a typical reversal of anisocoria in patients with Horner's syndrome. Moreover, apraclonidine was observed to have an elevating effect on the upper eyelid in Horner's syndrome as well as in healthy subjects, which is thought to be mediated by alpha-1 adrenergic receptors present in the Muller's muscle. We aim to quantitatively investigate the effect of apraclonidine on eyelid position in patients with Horner's syndrome compared to physiological anisocoria based on infrared video recordings from pupillometry. We included 36 patients for analysis who underwent binocular pupillometry before and after apraclonidine 1% testing for the evaluation of anisocoria. Vertical eyelid measurements were taken from infrared videos and averaged from multiple pupillometry cycles. Receiver operating characteristic curves were calculated to determine the optimal cutoff value for change in eyelid aperture pre- and post-apraclonidine. A decrease of inter-eye difference in the aperture of >0.42 mm was discriminative of Horner's syndrome compared to physiological anisocoria with a sensitivity of 80% and a specificity of 75%. Our data confirm an eyelid-elevating effect of the apraclonidine test, more pronounced in eyes with a sympathetic denervation deficit. Measuring eyelid aperture on pupillometry recordings may improve the diagnostic accuracy of apraclonidine testing in Horner's syndrome.

KEYWORDS

Apraclonidine test, Horner's syndrome, ptosis, anisocoria, Muller's muscle, eyelid aperture

Introduction

Apraclonidine has largely replaced cocaine as a pharmacological test in patients with Horner's syndrome by inducing a reversal of anisocoria (1–6). Apraclonidine, being an α2-agonist with weak α1-activity, causes a slight constriction of healthy pupils. Its dilating effect on the miotic pupil in Horner's syndrome results from denervation hypersensitivity to α1-adrenergic stimulation.

Moreover, apraclonidine has been observed to increase eyelid aperture in Horner's syndrome (5, 7), in botulinum toxin–induced ptosis (8), and in healthy subjects (9) presumably by an α1-receptor–mediated contraction of Muller's muscle. Muller's muscle, also named superior tarsal muscle, is a smooth muscle with adrenergic innervation, providing 1–3-mm eyelid elevation (10). The sympathetically innervated inferior tarsal muscle is the analogue in the lower eyelid, and its denervation accounts for a slight raise of the lower eyelid.

In a canine upper eyelid model, Yano et al. demonstrated that a selective α1A-adrenoceptor agonist indeed led to sustained Mueller muscle contraction similar to the effect of phenylephrine (11). A predominance of α1-receptors was also confirmed histopathologically in human ptotic eyelid specimens (12). In the same study, an inverse relationship was found between the eyelid elevation response to phenylephrine and the number of α2-receptors. The α2-receptor-mediated effect inhibits the release of norepinephrine at the synapses in the smooth muscle cells, therefore reducing the α1-mediated muscle contraction.

Considering the effect of apraclonidine on eyelid aperture may be particularly helpful as an adjunct in cases with equivocal pupillary response when pharmacological testing is performed. We aim to quantitatively investigate the effect of apraclonidine on eyelid aperture in patients with Horner's syndrome compared to physiological anisocoria based on infrared video recordings to determine the diagnostic accuracy of the eye-opening effect.

Materials and methods

Patients referred to the neuro-ophthalmology unit at the University Hospital Zurich for the evaluation of anisocoria from 2019 to 2021 were recruited consecutively for the study. Inclusion criteria were the presence of anisocoria more pronounced in the dark with or without ptosis and age >18 years. Exclusion criteria were previous ocular or eyelid surgery, ophthalmic treatment affecting pupil size or pupil motility, and conditions affecting pupillary reflexes including third cranial nerve palsy and pharmacological mydriasis.

All subjects underwent binocular pupillometry before and after pharmacological testing with apraclonidine 1% eye drops (one drop in each eye). The pupillometry test paradigm consisted of at least four cycles of 4-s light-on (3 log-lux) and 15-s light-off using a programmable desktop pupillometer [DP-2000, Neuroptics, Irvine, CA, USA (13)]. Pupillometry measures were taken from each eye simultaneously and in synchrony.

The diagnosis of Horner's syndrome was based solely on the response to apraclonidine testing irrespective of any causative lesion, the presence of ptosis, or heterochromia. The pupil size before and after apraclonidine instillation was calculated as the median size from 3 to 4 s after light-off derived from the pupillometry reading. The apraclonidine test was considered positive when the smaller pupil dilated and the larger pupil constricted, leading to a reversal of anisocoria or a convergence of pupil sizes indicative of Horner's syndrome. We excluded patients assessed at a latency >160 min after apraclonidine instillation, as the latter resulted in a negative correlation between the time elapsed and the effect on eyelid aperture.

The infrared videos recorded during pupillometry were analyzed using custom software (available upon request) written in MATLAB (Matlab 2019b, The MathWorks Inc., Natick, MA, United States). The pupil size in each eye was determined using our previously published method (13). For measuring the vertical palpebral aperture, a vertical line was preset through the center of the pupil. The intersection of the vertical line with the upper and lower eyelid margins was then determined manually, yielding the vertical eyelid aperture. The measurements were taken in a fixed interval within the first 5 s after light-off, avoiding blinks, and were averaged from three-to- four readings from individual pupillometry cycles. The inter-eye difference of vertical lid opening was calculated by subtracting the eye with the smaller pupil from the eye with the larger pupil. A paired t-test and linear correlation were used to compare the change of eyelid aperture and inter-eye difference pre- and post-apraclonidine using a threshold of $p<0.05$ for statistical significance. The receiver operating characteristic (ROC) curve using MATLAB was calculated to determine the optimal change of difference in eyelid aperture between the two eyes post-apraclonidine to differentiate Horner's syndrome from physiological anisocoria.

Written informed consent was obtained from all participants. The study was approved by the Zurich cantonal ethics committee, Switzerland (BASEC-Nr. 2016-02151) in adherence to the Declaration of Helsinki.

Results

Of 38 patients meeting the inclusion criteria, two were excluded due to dermatochalasis obscuring the eyelid margin, making the measurement impossible. The mean time elapsed between apraclonidine application and pupillometry was 57 min (range, 30–152 min). A total of 18 patients had a positive pupillary apraclonidine test, fulfilling the diagnostic criteria for Horner's syndrome, and 18 patients with a negative apraclonidine test were considered to represent physiological anisocoria.

The baseline characteristics of each group are summarized in Table 1. Figure 1 represents an example of left Horner's syndrome secondary to ipsilateral carotid artery dissection with a positive pupillary apraclonidine test. Eyelid aperture measurements pre- and post-apraclonidine in Horner's syndrome and physiological anisocoria are summarized in Table 2 and represented by box plots in Figure 2.

In Horner's syndrome, the mean eyelid aperture increased by 2.01 ± 1.06 mm (standard deviation) in the affected eye ($p<0.001$) and by 1.08 ± 0.88 mm in the non-affected eye ($p<0.001$). The

TABLE 1 Baseline characteristics.

	Horner's syndrome		Physiological anisocoria	
Subjects	n = 18		n = 18	
Mean age (years)	52.7 ± 21.9		39.3 ± 11.6	
Female : Male	5:13		10:8	
Pupil diameter 3–4 s after light-off (mean ± SD)	3.3 ± 0.5 mm (affected eye)	4.1 ± 0.5 mm (non-affected eye)	4.1 ± 0.8 mm (side of smaller pupil)	4.5 ± 0.8 mm (side of larger pupil)

inter-eye difference in eyelid aperture decreased significantly by -0.93 ± 0.80 mm ($p = 0.003$) (Figure 3A), and there was a significant correlation between the initial inter-eye difference and the change induced by apraclonidine ($r = 0.567$, $p = 0.014$).

In the group with physiological anisocoria, the mean eyelid aperture increased by 1.23 ± 0.80 mm in the eye with the baseline smaller pupil ($p < 0.001$) and by 1.12 ± 1.00 mm in the eye with the baseline larger pupil ($p < 0.001$). The inter-eye difference in

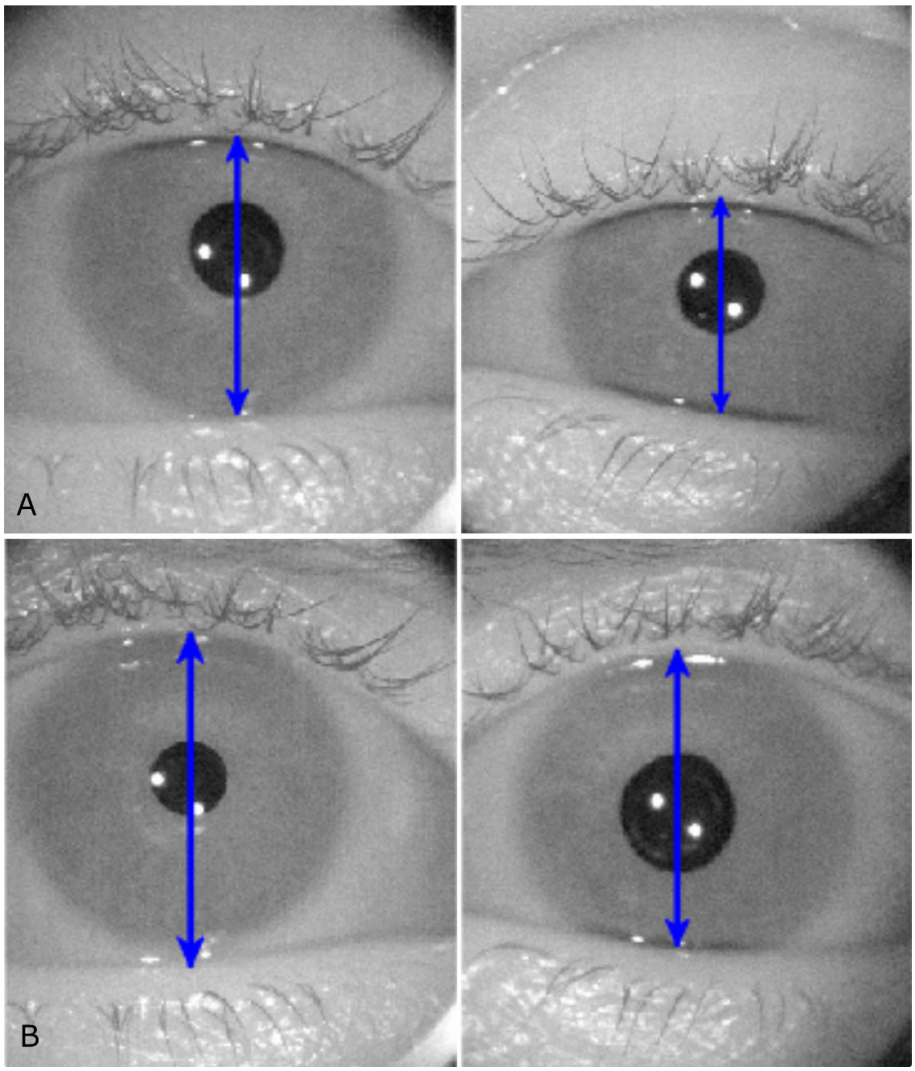

FIGURE 1
(A) Infrared images from pupillometry recordings showing the narrowing of eyelid aperture and miosis on the affected left side in a patient with Horner's syndrome. **(B)** Approximately 30 min after apraclonidine 1% instillation, the left > right eyelid elevates and anisocoria reverses. Blue arrows correspond to the vertical eyelid aperture.

TABLE 2 Mean eyelid aperture measured before and after apraclonidine application.

	Horner's syndrome		Physiological anisocoria	
Side	Affected eye	Non-affected eye	Side of smaller pupil	Side of larger pupil
Eyelid aperture, before apraclonidine (mean ± SD)	9.9 ± 1.1 mm	10.8 ± 1.2 mm	9.8 ± 1.7 mm	9.9 ± 1.4 mm
Eyelid aperture, after apraclonidine (mean ± SD)	11.9 ± 1.2 mm	11.9 ± 1.6 mm	11.0 ± 1.5 mm	11.0 ± 1.1 mm

eyelid aperture did not change (-0.1 ± 0.44 mm, p = 0.669) (Figure 3B), and there was no correlation between the initial inter-eye difference and the change induced by apraclonidine (r=0.013, p=0.958).

ROC curves to define the optimal cutoff value for post-apraclonidine eyelid aperture were calculated either based on change in inter-eye aperture difference (Figure 4A) or based on the increase of aperture on the affected (baseline smaller pupil) or non-affected side (baseline larger pupil), respectively (Figure 4B). For the inter-eye aperture difference, the area under the ROC curve was 0.73, and the best sensitivity of 80% and specificity of 75% was obtained with a cutoff value of >0.42 mm change in inter-eye aperture difference. When measuring only the eyelid aperture of the affected eye, the resulting area under the ROC curve was 0.72, with a sensitivity of 80% and specificity of 70% for a cutoff value of 1.45mm. For the non-affected eye, the area under the ROC curve was 0.52.

Discussion

Our data show a diagnostically relevant eye-opening effect of topical apraclonidine. The eyelid aperture increased in all subjects irrespective of the presence of Horner's syndrome and most significantly in eyes affected by the condition. Apraclonidine does not induce a "reversal of ptosis" in analogy to the "reversal of anisocoria" in patients with Horner's syndrome, but as the inter-eye difference decreases, a positive apraclonidine test results in a nearly symmetrical eyelid position. Similar to the denervation hypersensitivity to the α1-stimulation of the pupil dilator muscle (1), there may be an upregulation of α1-adrenergic receptors in the Muller's muscle, leading to the overproportionate response to apraclonidine. It is possible that the response is further enhanced by a downregulation of α2-receptors, reducing their inhibiting effect on sympathetic stimulation. In Horner's syndrome, the well-recognizable mean increase of eyelid aperture was 2.0 mm in our cohort.

In eyes not affected by Horner's syndrome, we found an increase of eyelid aperture of approximately 0.9–1.0 mm, similar to the effect of 0.7 mm found in healthy subjects by Kirkpatrick et al. (9) Because upper eyelid height was measured relative to the central pupillary light reflex in their study, the results are likely to differ slightly as the contribution of the inferior tarsal muscle to total eyelid aperture is not taken into account. To our knowledge, no studies have addressed the effect of apraclonidine on ptotic eyelids in the context of parasympathetic denervation (third nerve palsy), ocular myasthenia gravis, or levator

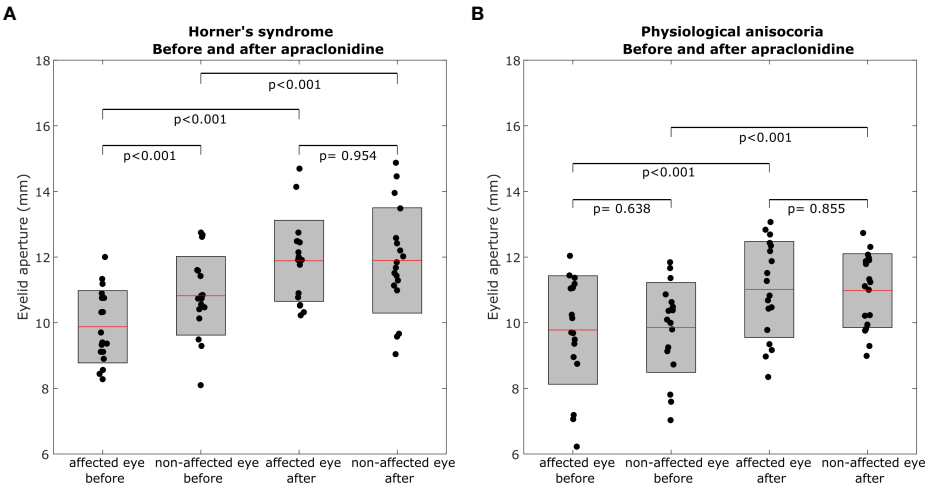

FIGURE 2
Box plots representing eyelid aperture pre- and post-apraclonidine in Horner's syndrome **(A)** and physiological anisocoria **(B)**. Central red mark = mean, box boundaries = 25–75th percentiles.

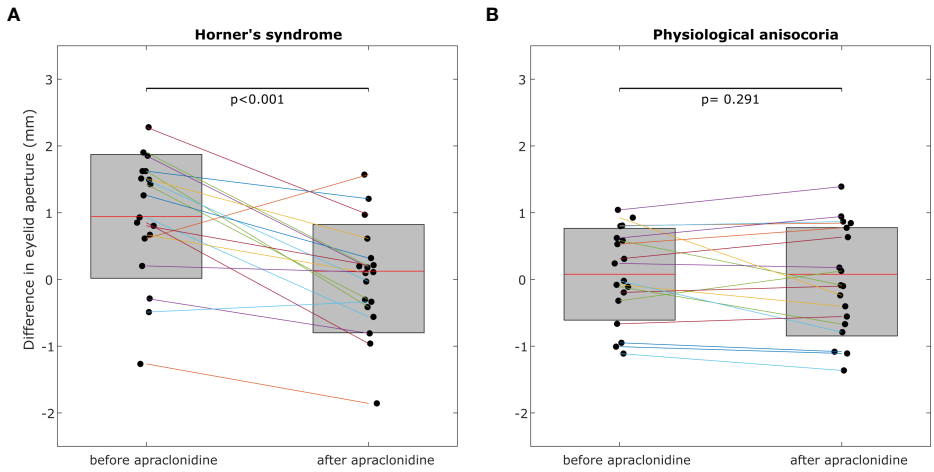

FIGURE 3
The inter-eye difference of eyelid aperture decreases significantly post-apraclonidine in Horner's syndrome **(A)** but not in physiological anisocoria **(B)**. Central red mark = mean, box boundaries =25–75th percentiles.

dehiscence so far. It remains unanswered whether these disorders influence the adrenergic receptor expression in the Muller's muscle and if, as a consequence, apraclonidine might be useful in the differential diagnosis.

We found that comparing the inter-eye difference pre- and post-apraclonidine and measuring the affected eye alone, i.e., only the eyelid on the side of the smaller pupil, yields similar results (area under the ROC curve 0.821 versus 0.725, respectively). As expected, measuring the aperture of the non-affected eye, that is, the eye with the baseline larger pupil, does not help to distinguish Horner's syndrome from physiological anisocoria (area under the ROC curve close to 0.5). The inter-eye difference is less prone to influencing factors on eyelid opening, such as general alertness or possible squinting due to photophobia or dry eye sensation, which would affect both eyes equally. A decrease of inter-eye difference by more than 0.42 mm after apraclonidine instillation is suggestive of Horner's syndrome with a sensitivity of 83% and specificity of 78%. Combining the analysis of eyelid aperture with the change of pupil size after pharmacological testing with apraclonidine is

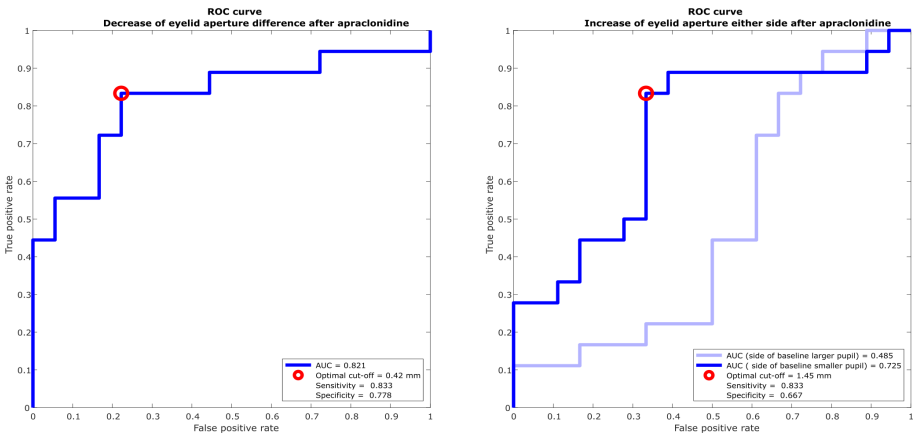

FIGURE 4
Receiver operating characteristic (ROC) curves for discriminating Horner's syndrome from physiological anisocoria. **(A)** The optimal cutoff value for change in inter-eye difference of vertical eyelid opening post-apraclonidine is 0.42 mm with a sensitivity of 83% and specificity of 78%. **(B)** The optimal cutoff value for change in eyelid aperture of the eye with the baseline smaller pupil is 1.45 mm with a sensitivity of 83% and specificity of 67%. The change of eyelid aperture in the eye with the baseline larger pupil is not diagnostically helpful with an area under the ROC curve of nearly 0.5.

expected to increase the diagnostic accuracy even further. Manual determination of eyelid aperture by an unmasked investigator may constitute a source of confirmation bias in our study, which was minimized by averaging several measurement cycles.

It was previously suggested that apraclonidine may be useful to correct inadvertent, transient botulinum toxin–induced ptosis (8). It remains unknown whether regular apraclonidine application would represent a long-term treatment option for ptosis in Horner's syndrome. A high rate of tachyphylaxis occurs when apraclonidine is used as an intraocular pressure–lowering agent beyond 3–6 weeks of use (14), and the same might apply to its effect on smooth muscle.

Precise measurement of eyelid aperture in clinical practice is hardly possible without image documentation. Performing the measurements on video recordings offers a feasible approach amenable to the clinical routine if pupillometry is performed. Measuring the effect of apraclonidine on the eyelids may be particularly useful when pupillary measurements are unreliable, such as in post-traumatic or postoperative pupillary damage. When used in addition to analyzing the effect of apraclonidine on the pupillary size, measuring the effect on eyelid aperture may further increase the diagnostic accuracy in evaluating Horner's syndrome.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was reviewed and approved by Kantonale Ethikkommission Zürich, Switzerland. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FF: study design, data collection, data analysis, and paper writing; LD: data collection, data analysis, and paper revision; CB: data analysis and paper revision; KW: study design, data analysis, and paper revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ocular myasthenia gravis saccades as a measure of extraocular muscle function

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Background: It is important to understand the pathophysiology of ocular myasthenia gravis (OMG) to improve treatment.

Aim: To use modern video-oculography to characterise saccadic eye movements in patients with OMG, including anti-AChR, anti-MuSK, anti-LRP4, and seronegative OMG.

Methods: In total, 21 patients with OMG and five age-matched healthy control subjects underwent video-oculography. Participants performed a sequence of horizontal saccades (3 minutes each) at ±5°, ± 10°, and ±20°, followed by 3 minutes of saccades directed at randomly presented targets at ±5°, ± 10°, and ±15°. We recorded the direction, amplitude, duration, peak, and average velocity of each saccade for each task for each participant.

Results: Saccadic amplitude, duration, and average velocity were all lower in OMG patients than in control subjects ($p < 0.021$). Saccadic amplitude and velocity decreased over time, but this decrease was similar in OMG patients and control subjects. Fixation drift and ocular disparity tended to be greater in OMG patients than in control subjects. Saccadic intrusions occurred more frequently in OMG patients than in control subjects ($p < 0.001$). No significant effects of time or group by time on fixation drift or ocular disparity were found.

Discussion: Saccadic velocities in OMG patients differed from those in normal control subjects, which suggests that OMG affects fast-twitch fibres, although fast-twitch fibres were still able to generate "twitch" or "quiver" movements in the presence of even severe ophthalmoplegia. Slow-twitch muscle fibres involved in gaze holding were also affected, accounting for increased fixation drift following saccades. Our objective finding of increased fixation drift and a larger number of saccadic intrusions mirror

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our anecdotal experience of patients with OMG who report significant diplopia despite minimal ophthalmoplegia on examination. Such microsaccades may be a surrogate for compensation of a gaze-holding deficit in MG.

KEYWORDS

ocular myasthenia gravis, extraocular muscle, myasthenia gravis, saccades, video-oculography

Introduction

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction that presents initially with ocular symptoms in 80%–85% of patients (1, 2). Up to 40%–70% of these patients may have ocular symptoms only (1, 3), i.e., ocular myasthenia gravis (OMG). The ocular symptoms of diplopia and ptosis can be disabling and adversely affect a patient's quality of life (4). Therefore, an understanding of the pathophysiology underlying these ocular symptoms is important for the advancement of treatment and development of patient-centred care in MG.

The hallmarks of MG are the variability of symptoms and signs of neuromuscular weakness. Classical ocular symptoms of MG (5) include the Cogan's lid twitch and "quiver", or twitch-like movements in paretic muscles (6). Although "lid twitch" is not specific to MG (7), a prerequisite of Dr. Cogan's original definition of MG is the presence of ptosis. This suggests a differential impact of MG in the extraocular muscle (EOM) fibres, with relative preservation of fast-twitch muscle fibres.

Previous studies of eye movement in MG (i.e., not limited to OMG) have shed some light on the pathophysiological effects of MG on ocular muscles, e.g., preservation of high-velocity saccades in the presence of severe ophthalmoplegia, indicating selective impairment of tonic fibres (8, 9), and variability of saccades (10, 11). However, there remains much to be elucidated, as EOMs contain six muscle fibre types distributed according to the different layers and are recruited at different phases of eye movements (12, 13).

In addition, mapping eye movement studies with the clinical phenotype may be helpful to further understand the pathophysiology of OMG. The pathogenic antibodies in MG include antibodies against the acetylcholine receptor (anti-AChR), muscle-specific kinase (anti-MuSK), and low-density lipoprotein receptor-related protein 4 (anti-LRP4). However up to 40%–50% of patients with OMG are seronegative, of whom approximately 50% have been found to produce anti-AChR antibodies; more recently, it has been found that a smaller percentage produce anti-MuSK and anti-LRP4 antibodies (14, 15). The clinical observation that OMG patients who produce anti-AChR antibodies have more severe ophthalmoplegia and ptosis than seronegative OMG patients suggests that different types of EOM muscle fibres are affected (unpublished observation, SHW).

This preliminary study aims to characterise saccadic eye movements across all OMG phenotypes, including anti-AChR, anti-MuSK, anti-LRP4, and seronegative OMG, with a focus on fixational eye movement abnormalities.

Methods

Participants and apparatus

Twenty-one participants with MG (11 with anti-AChR OMG, 1 with anti-LRP4 OMG, 1 with anti-MuSK OMG, 7 with seronegative OMG, and 1 with anti-AChR secondary generalised MG) were prospectively identified and recruited from the OMG clinic at Moorfields Eye Hospital NHS Foundation Trust. All participants underwent a full clinical examination (orthoptics, neuro-ophthalmology, and general medical assessment) to confirm their diagnosis. Ten control participants were recruited from staff members at Moorfields Eye Hospital NHS Foundation Trust and University College London. After providing informed written consent, participants underwent infrared video-oculography using an EyeLink 1000 eye tracker (SR Research, Ottowa, ON, Canada). We recorded the position of both eyes (where possible) at a sampling rate of 500 Hz while participants performed a range of saccadic tasks. Stimuli were presented on an Eizo Flexscan EV2736W LCD monitor, with 2560 × 1440 pixel resolution, 60 Hz refresh rate, and a physical panel size of 59.7 cm × 33.6 cm. The monitor was calibrated using a Minolta photometer, with luminance linearised by software to give a maximum of 150 cd/m^2. Participants were positioned with their heads lying on a chin rest, and a forehead bar was applied to minimise head movement. The viewing distance was 75 cm. Stimulus presentation was binocular for all participants and monocular when a large degree of strabismus was present and the eye tracker was unable to record the fellow eye. Participants requiring refractive correction wore their usual spectacles.

Stimuli and procedures

Before gaze data were recorded, participants performed a binocular five-point calibration, where possible. If this was not possible, monocular calibration of the dominant eye was carried out.

Participants performed the following sequence of saccade tasks, each of which lasted for 3 minutes: horizontal ±5°, vertical ±5°, horizontal ±10°, vertical ±10°, horizontal 20°, vertical 20° (20° steps between ±10° locations), followed by 3 minutes of horizontal saccades with randomly presented targets at ±5°, ± 10°, and ±15°, and 3 minutes of vertical saccades with randomly presented targets at ±5° and ±10°. A red circle subtending approximately 0.5° of visual angle was used as the target stimulus on a mid-grey background. The target was shown for 3 seconds at each location. Participants were allowed to rest for an adequate period between each block of trials (minimum rest time of 60 seconds). All procedures were approved by the Wales REC 6 Research Ethics Committee (IRAS 279233).

Data analysis

The EyeLink 1000 eye-tracking software parses the gaze data into saccades and fixations using a saccade-picking algorithm. Saccade onset is defined as the point at which velocity exceeds a threshold of 30° per second or the point at which acceleration exceeds a threshold of 8000°/s^2, and saccade offset is defined as the point at which velocity falls below the threshold. Saccade onset defines fixation offset and vice versa. Data Viewer software (version 4.2.1, SR Research) was used to output the direction, amplitude, duration, peak, and average velocity of each saccade for each task and each participant. Saccades of <2°, saccades that contained blinks, and saccades that had a greater vertical than horizontal amplitude were excluded from the main analysis. In this way, all leftward/rightward saccades of >2° were examined, irrespective of their relationship with the target step.

For each task, saccades were grouped into three time bins, corresponding to the first, second, and third minute of the tasks.

To examine fixation stability, two separate analyses were performed. In the first analysis, monocular data were used, and the horizontal difference in gaze location at the start and end of each fixation of >100 ms in duration was taken as a measure of drift. In the second analysis, binocular data (available from 17/21 patients and all controls) were used, and the difference in average gaze location between the left and the right eyes during all fixations was taken as a measure of ocular disparity. Drift and ocular disparity were reported in degrees of visual angle.

Square wave jerks (SWJs), a type of saccadic intrusion, were defined as saccades of <2° that were followed within 300 ms by another saccade of <2° in the opposite direction (Leigh and Zee, 2006). The number of SWJs across all tasks was counted for each participant.

Data were statistically analysed in SPSS 28.0 (IBM Corp.). Fixation stability and saccadic metrics were analysed by repeated-measures ANOVA, with the between-subject factor group (OMG vs. control) and the within-subject factor of time (first vs. second vs. third minute). Greenhouse–Geisser correction was used when Mauchly's test of sphericity was significant. The difference between groups (OMG vs. control) in the number of SWJs was analysed by Mann–Whitney *U*-test owing to data deviating from normality. Identical results were obtained when normalising the number of SWJs by the total number of saccades; non-normalised data are reported for ease of interpretation. Statistical significance was set at 0.05 after correction for multiple comparisons using Bonferroni adjustment. Summary statistics are presented as mean ± 1 SE for fixation stability and saccadic metrics, and median ± interquartile range (IQR) is presented for SWJs.

Results

Figure 1 shows group summary statistics of all saccadic metrics over time. Saccadic amplitude, duration, and average velocity were lower in OMG patients than in control subjects [6.5° ± 0.3° vs. 9.1° ± 0.5°, 45.2 ± 1.5 vs. 53.5 ± 2.2 ms, 164.0° ± 3.5° vs. 188.9° ± 7.1° per second, respectively; all $F(2,30) > 5.9$, $p < 0.021$]. Saccadic peak velocity did not statistically differ between groups [OMG: 282.3° per second ± 14.1° per second; control: 318.7° per second ± 21.0° per second; $F(1,30) = 2.0$, $p = 0.161$] but tended to be smaller in OMG patients than in control subjects. Saccadic amplitude, average velocity, and peak velocity decreased over time [all $F(2,60) > 4.2$, $p < 0.02$] but this decrease did not differ between groups [time × group: $F(2,48) = 1.3$, $p = 0.287$]. *Post-hoc* tests revealed statistical differences between the first and the third minute after adjustment for multiple comparisons (amplitude: 8.2° ± 0.4° vs. 7.5° ± 0.3°, $p = 0.034$; average velocity: 168.3° per second ± 5.3° per second vs. 158.1° per second ± 5.0° per second, $p = 0.002$; peak velocity: 310.9° per second ± 13.4° per second vs. 292.7° per second ± 13.3° per second, $p = 0.010$). No significant effect of time or interaction between time and group was found on saccadic duration [all $F(2,60) < 1.7$, $p > 0.2$].

Figure 2 shows example gaze traces and group summary statistics of fixation stability. Fixation drift and ocular disparity were generally greater in OMG patients than in control subjects (0.24° ± 0.02° vs. 0.16° ± 0.04°; 0.6° ± 0.1° vs. 0.2° ± 0.2°, respectively) but the differences were not statistically significant [$F(1,29) = 3.3$, $p = 0.080$, and $F(1,24) = 2.7$, $p = 0.114$, respectively]. No significant effects of time or group by time were found on fixation drift and ocular disparity (all $p > 0.3$).

The number of SWJs (median [IQR]); was significantly larger in OMG patients than in control subjects [OMG: 145.5 [84 272]; control: 32.5 [22 85] $U = 223$, $z = 3.29$, $p < 0.001$]. Figure 3 shows an example of increased SWJ

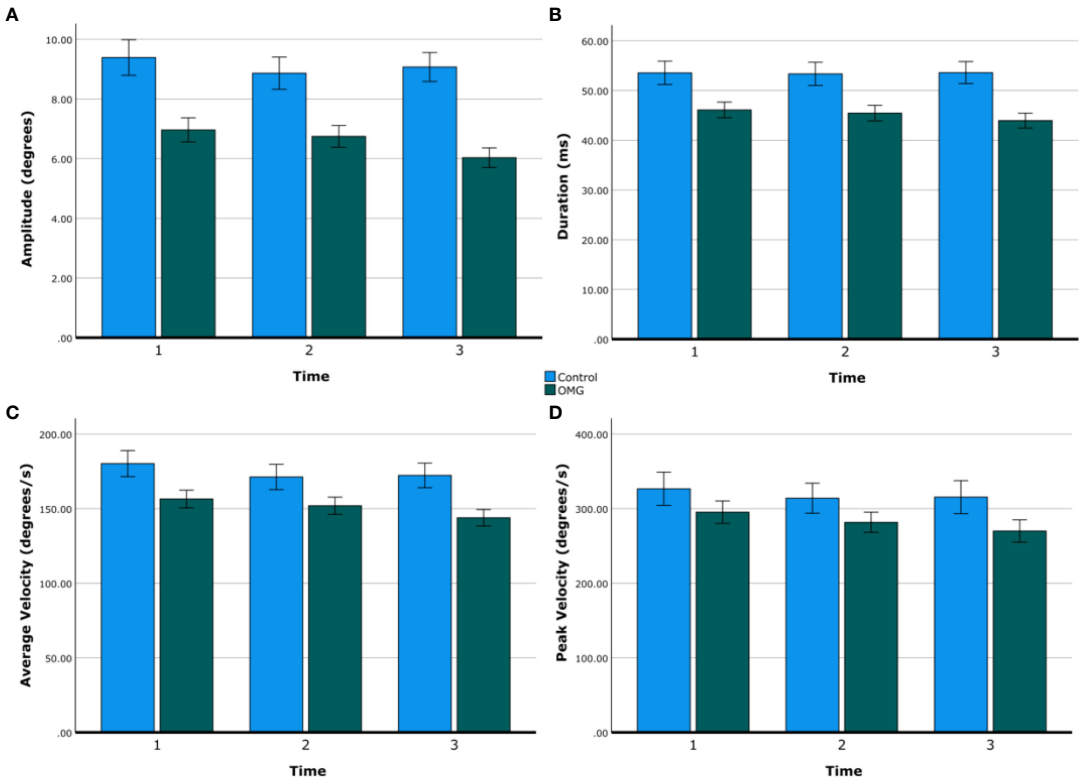

FIGURE 1
Saccadic metrics over time. Group means of saccadic amplitude **(A)**, duration **(B)**, average velocity **(C)**, and peak velocity **(D)** over time (first, second, and third minute) in control subjects (blue) and OMG patients (green). Error bars are ±1 SE.

frequency for one control (Figure 3A) and OMG (Figure 3B) participant, and the distribution of all counted SWJs for each group (Figure 3C).

Discussion

This preliminary study using state-of-the-art modern oculography adds to our knowledge of OMG, as only a few oculography studies have been conducted previously (6, 8, 10, 11, 17, 18). Overall, the number of saccadic intrusions during attempted steady fixation in patients with OMG was twice that of control subjects. OMG patients also showed a tendency to dysconjugate ocular drift between left and right eyes following large horizontal saccades; this has not, to our knowledge, been previously described in patients with this condition.

We also observed reduced saccadic amplitude and velocity in OMG patients compared with control subjects, in keeping with previous observations that slow-twitch (tonic) muscle fibres are preferentially affected in MG (8, 9, 11, 17). Saccades in the third minute were significantly smaller than those in the first minute of recording in OMG patients, consistent with fatigue, but velocity did not decrease. Unlike previous reports, we found saccadic velocities to be significantly lower in OMG patients than in control subjects (8), indicating at least some involvement of fast-twitch fibres. However, such fibres appear sufficient to generate "twitch" or "quiver" movements in the presence of severe ophthalmoplegia, a characteristic feature of MG (8). A recent study using video-nystagmography found a decrement in EOM activity in patients with MG that improved within 1–2 seconds after reaching minimum velocity (19). This is in keeping with our findings that MG affects saccades.

A range of saccadic intrusions were described by Smidt and colleagues in a study of 12 patients with OMG, including a saccadic pulse (stepless saccade) with an exponential decay back to the baseline, a double saccadic pulse, SWJs, macro-SWJs, and macro-saccadic oscillations (8). We did not systematically classify these in our study but noted a similar range of intrusions across OMG subtypes. Although saccadic intrusions are a feature of many cerebellar disorders, such as Friedreich's ataxia (20), recent oculomotor models propose that they are the result of dysfunction within the brainstem ocular motor network (21), which includes excitatory burst neurons (EBNs), inhibitory burst neurons (IBNs), omnipause neurons (OPNs), and their connections with the superior colliculus (SC). Increased fluctuation of neural activity within the SC is thought to

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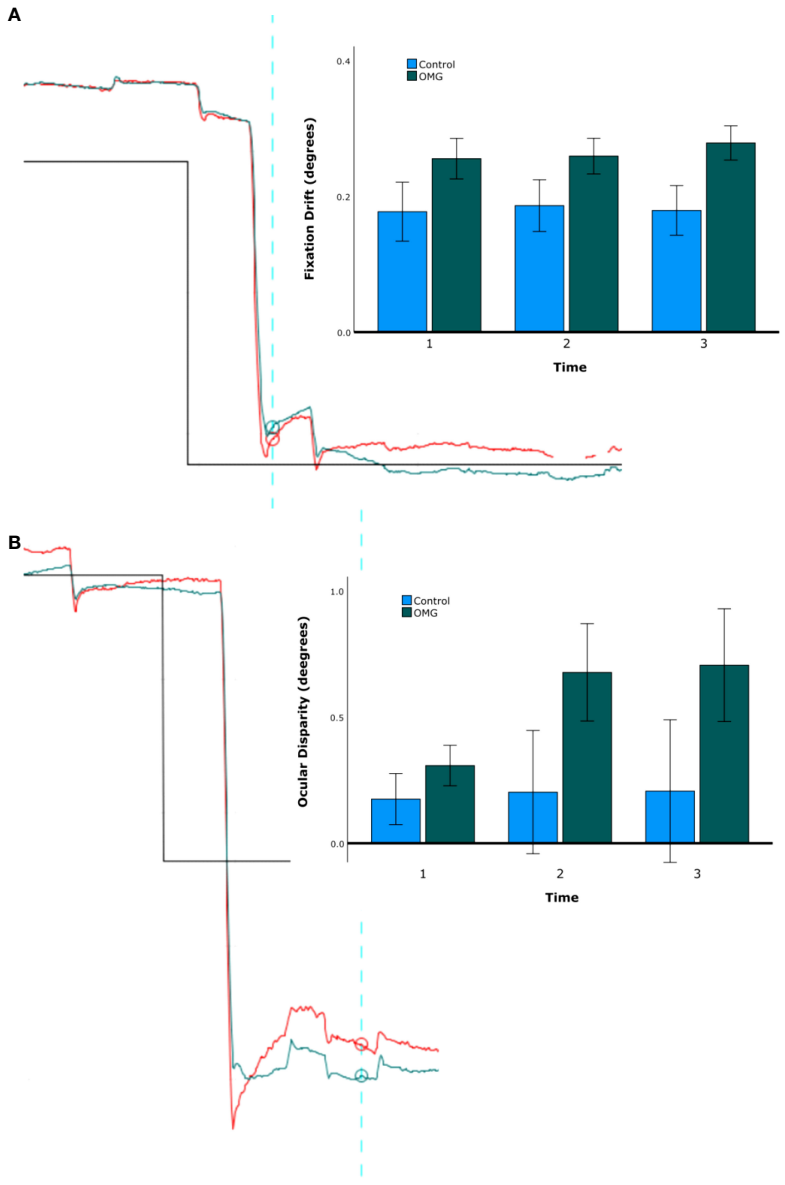

FIGURE 2
Fixation stability. Fixation drift **(A)** and ocular disparity **(B)**. The traces on the left-hand side of A and B shows the right (red) and left (green) gaze position (*y*-axis) over time (*x*-axis) for one representative OMG patient with abnormal signs and symptoms. The upward direction in the graph represents the leftward gaze, downward direction represents the rightward gaze. Note the difference in gaze position between the start (blue vertical line) and the end (furthest right time point) of fixation in A and the difference in gaze position between the right and the left eyes over time in **(B)**. Note also the hypometria with glissade, implying a pulse-step mismatch and a recognised feature of OMG (16). The bar charts on the right-hand side of A and B show group mean ($\pm$ 1 SE) fixation stability over the three time bins (first, second, and third minute) for OMG patients (green) and control subjects (blue).

increase input to EBNs and decrease input to OPNs, leading to a short burst of activity in the EBNs that produces a small saccade (21). In turn, this produces a small retinal error that is detected in the SC network and results in a second saccade in the opposite direction, generating a SWJ. The cerebellar fastigial nucleus has direct projections to IBNs that may modify the brainstem ocular motor network. Saccadic intrusions in OMG may instead reflect centrally mediated attempts to correct fixational instability related to abnormal gaze holding (8). It has been suggested that micro-SWJs may be a physiological response to impaired gaze fixation, increasing in amplitude with larger fixation targets and in darkness (22). This could account for the presence of SWJs in healthy individuals (e.g. with fatigue or altered fixation target) and in neurological disorders with impaired tonic gaze

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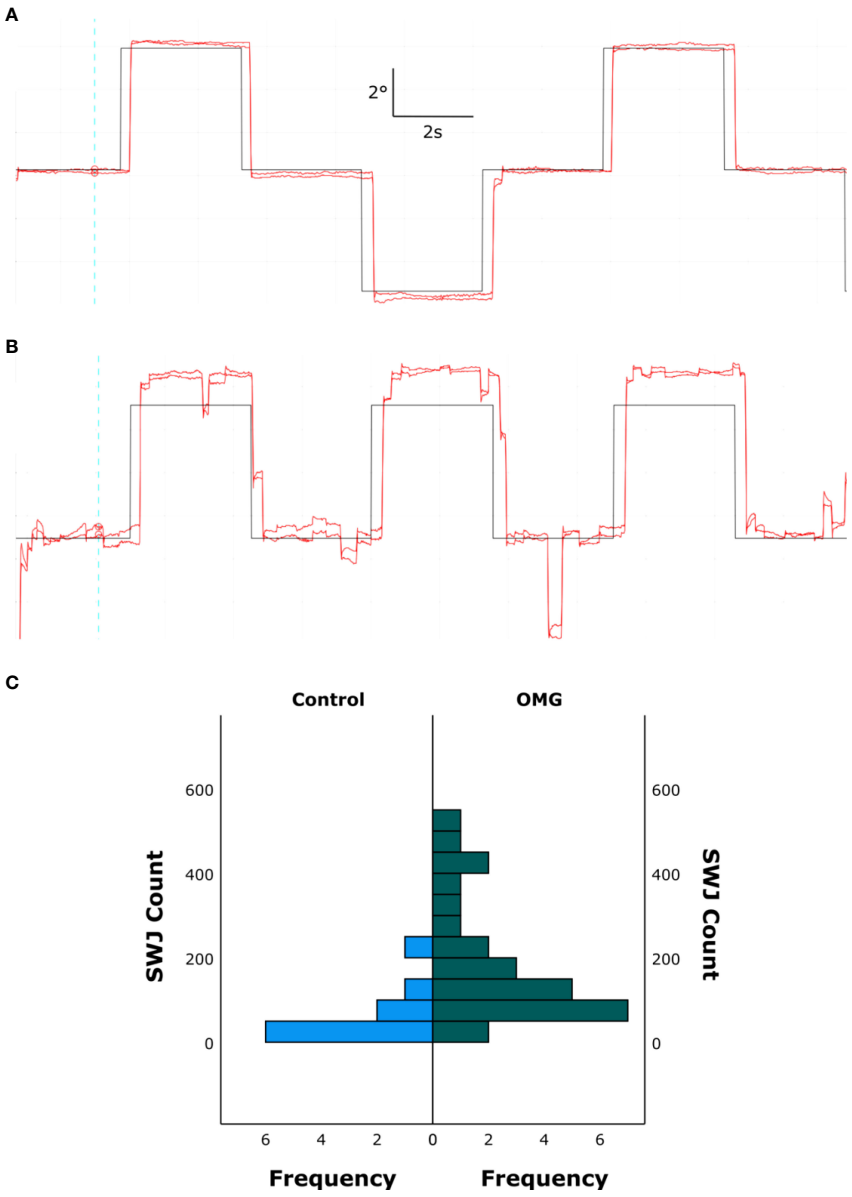

FIGURE 3
Square wave jerks. Binocular gaze position (red) over time in one control subject **(A)** and one OMG patient with abnormal signs and symptoms **(B)** making saccadic movements to targets at ±5° from the primary position. Target location over time is depicted in black. The upward direction in the graph represents leftward gaze, downward direction represents rightward gaze. Note the increased frequency of SWJs during fixation in B compared with A. **(C)** Histogram showing all counted SWJs for all control subjects (left, blue) and OMG patients (right, green).

holding (e.g. MG, brainstem disease, and cerebellar disease). Indeed, this is in accord with our observation that fixation drift tends to be increased in patients with OMG. Given a tendency for each eye to show a different degree of drift following a saccade, further research should explore differences in SWJ frequencies between the right and left eyes. Our objective finding of fixation drift and saccadic intrusions mirrors our anecdotal experience of patients with OMG who have symptomatic diplopia but in whom examination reveals only minimal ophthalmoplegia. Such intrusions may be a surrogate measure of central compensation for this gaze-holding deficit.

This preliminary study has a number of limitations. First, although we aimed to include patients with the range of OMG subtypes, there were insufficient numbers of patients with each subtype for us to carry out independent comparisons of subtypes. Second, we were able to recruit only 10 healthy

control participants owing to the COVID-19 pandemic and constraints on healthy individuals attending clinical care settings during this time. Third, we were unable to systematically analyse the range of saccadic intrusions owing to the variability of intrusion waveforms between and within individuals with OMG. Instead, we opted to categorise saccadic intrusions based on other oculographic studies in patients with neurological disorders and the known characteristics of SWJs (23–25).

Future studies should further explore the characteristics of saccadic intrusions, with a focus on interocular differences and the timing of these intrusions relative to the saccadic movements (e.g. pre, per, or post). Moreover, our study was insufficiently powered to identify whether or not such oculomotor abnormalities differ between seropositive and seronegative OMG groups, and whether or not such findings correlate with anecdotal findings that seropositive OMG patients manifest more severe ophthalmoplegia than seronegative individuals who have more variable and less severe ophthalmoplegia.

Conclusions

Here we report on one of the largest cohorts of OMG patients, exploring saccadic and fixational eye movement abnormalities. Our data on saccadic eye movements show that the fast-twitch fibres in OMG are affected, with amplitude, duration, and average velocity all reduced compared with normal control subjects. We found a trend towards increased saccadic intrusions and propose that these may reflect a central mechanism of compensation for gaze-holding deficits. Understanding the characteristics of these abnormalities and how they correlate with clinical features, such as diplopia, may help us further understand the pathophysiology of OMG and its impact on an individual's day-to-day function.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Wales REC 6 Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SW – design of the study, data analysis, writing of the manuscript, and principal investigator for the study. MB – data analysis, and writing and review of the manuscript. VT-H – design of the study, data collection, and writing and review of the manuscript. MA – data collection and review of the manuscript. AK – data collection and review of the manuscript. CN – data collection and review of the manuscript. MT – design of the study and review of the manuscript. DK – design of the study, data analysis, and review of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of acetazolamide on linear growth in children with pseudotumor cerebri syndrome

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Background/introduction: While oral acetazolamide is a cornerstone of management of adult and pediatric PTCS, previous studies have suggested that acetazolamide used in children with other conditions may influence growth.

Aims and methods: Retrospective chart review involving a single tertiary medical center. Thirty-four children with definite or probable PTCS were identified. Analysis was restricted to individuals from whom anthropometric data were available *before* and *during* acetazolamide treatment (n=22).

Results: Half of individuals (n=11/22) showed a decline in BMI Z-scores. Sixty-three percent (n=14/22) showed a decrease in height Z-scores during treatment with acetazolamide; in 6 of these 14 children who had complete data, 3 showed at least a partial recovery of height Z-scores after discontinuation of acetazolamide.

Conclusion: Acetazolamide may be associated with growth suppression in some children treated for pediatric PTCS. In some cases, the growth suppression appears to reverse once the acetazolamide is stopped.

KEYWORDS

acetazolamide, pseudotumor cerebri (PTC), idiopathic intracranial hypertension (IIH), weight, growth

Introduction

Pseudotumor cerebri syndrome (PTCS) encompasses the constellation of symptoms caused by elevated intracranial pressure of unclear etiology with normal brain parenchyma and cerebrospinal fluid constituents (1). Pediatric PTCS shares some, but not all, features of its adult counterpart. For example, previous studies suggested age, sex, and pubertal status influence the epidemiology of pediatric PTCS (2–6). Both female sex and obesity appear to be

more strongly associated with PTCS in older, but not younger, pediatric patients (2, 7). In addition, further analysis has characterized subgroups of pediatric PTCS: a 'young' cohort, with normal height and weight, an 'early adolescent' cohort who are typically overweight, and a 'late adolescent' cohort who are typically obese (8).

While oral acetazolamide is a cornerstone of management of adult and pediatric PTCS, previous studies have suggested that acetazolamide used in children with other conditions may influence weight gain and growth (9, 10). One study retrospectively reviewed medical records of children (n=22, age range 2 months to 15 years) on acetazolamide for management of glaucoma. Nine percent showed a decline in weight gain which crossed at least two growth percentile categories (e.g., from 50th percentile to <10th percentile) during acetazolamide treatment (9). In a second study (n=17 subjects, age range 1.2 – 6.5 years), the use of acetazolamide, as an adjunct management of epilepsy, was associated with a significant decrease in both height and weight standardized scores (10).

While adults with PTCS on acetazolamide do not have to be concerned about growth suppression, this potential side effect would be disconcerting to growing children with PTCS and their parents. Our study examines the effects of oral acetazolamide on pediatric growth parameters during treatment for PTCS.

Methods

This study is a retrospective chart review involving a single tertiary medical center. Institutional Review Board (IRB)/Ethics Committee approval was obtained (Children's Hospital of Philadelphia (IRB# 13-010158). Patient charts were identified *via* an electronic medical record search for ICD-9 code 348.2 and/or patient database of a single pediatric neuro-ophthalmologist (GTL). For this pediatric study, only patients aged 2 to 18 years at diagnosis were included in the study, as we considered the pathophysiology of this diagnosis in infancy to be distinct. Cases of definite or probable PTCS were collected, as previously described (1, 8). Cases of primary PTCS (also known as idiopathic intracranial hypertension, IIH) and secondary PTCS were included. Retrospective data were collected on patients seen between July 1993 and April 2013 as part of a previous study (8), using manual and bioinformatics-based abstraction. During chart review, all available measurements of height and weight were collected, at time points prior to and following the diagnosis of PTCS until April 2013.

Analysis was limited to subjects with ≥ 5 growth parameter measurements over time and clear documentation of acetazolamide use, with standard oral dosing of 15-20 mg/kg/day divided into two or three doses. For each case, age and anthropometric measurements were documented according to U.S. CDC 2000 growth standards (11). Anthropometric measurements included height Z-scores, weight Z-scores, and body mass index (BMI) Z-scores. BMI Z-scores were categorized as obtained prior to, during, and after discontinuation of acetazolamide. Where more than one measurement was available, mean data was reported and included for analysis. As in previous studies, pediatric obesity was defined using BMI Z-score. Overweight and obese were defined according to the CDC classifications of overweight (BMI percentile for age and sex ≥ 85 and < 95, corresponding to BMI Z-score ≥ 1.04 and < 1.64) and obese (BMI percentile for age and sex ≥ 95, corresponding to BMI Z-score ≥ 1.64) in children. Study data were collected and managed using REDCap (Research Electronic Data Capture) tools (12) hosted at The Children's Hospital of Philadelphia.

Results

Using updated PTCS diagnostic criteria (1), we identified 34 pediatric subjects with definite or probable PTCS treated with acetazolamide, of whom 29 were diagnosed with primary PTCS. The other 5 were diagnosed with secondary PTCS (three had renal failure, one used doxycycline, and the other was withdrawn from chronic corticosteroids). Subjects were 59% female with a mean age at diagnosis of 12.5 ± 4.1 years and mean BMI Z-score at diagnosis of 1.16 ± 1.1 (mean ± standard deviation, Table 1). The duration of acetazolamide treatment ranged from 49 – 982 days, with a median of 201 days. For subjects with anthropometric data available *before* and *during* acetazolamide treatment (n=22), there was no obvious trend in change in BMI Z-score as half subjects showed a decline in BMI Z-scores (n=11/22), while the other half had an increase in BMI Z-score (Figure 1A). In addition, 63% of subjects showed a decrease in height Z-scores during treatment of acetazolamide (n = 14/22) (Figure 1B).

We questioned whether that the effects of acetazolamide on weight gain and growth might depend on baseline nutritional status or age, but some children who were of normal weight or less (ie. BMI Z-scores <1.04) and/or young (age <10) experienced a decrease in height Z-score, while there were others who had an increase in height Z-score (Figure 1B).

Limited paired data were available for children before, during and after discontinuation of treatment (*n*=8, with > 1 measurement of anthropometric before, during, after discontinuation treatment with acetazolamide; follow-up anthropometric data was obtained after

TABLE 1 Initial demographics and anthropometrics of pediatric subjects diagnosed with PTCS and included in the evaluation of the effect of acetazolamide on growth parameters.

Characteristic	
Sex (% female, n)	59% (20/34)
Age (yrs)	12.5 ± 4.1
Height	
Height (m)	1.49 ± 0.21
Height Z-score	0.46 ± 1.22
Weight	
Weight (kg)	62.8 ± 29.2
Weight Z-score	1.34 ± 0.97
BMI	
BMI (kg/m^2)	25.3 ± 8.4
BMI Z-score	1.16 ± 1.10

Summary outcomes for continuous variables are presented in means ± standard deviation.

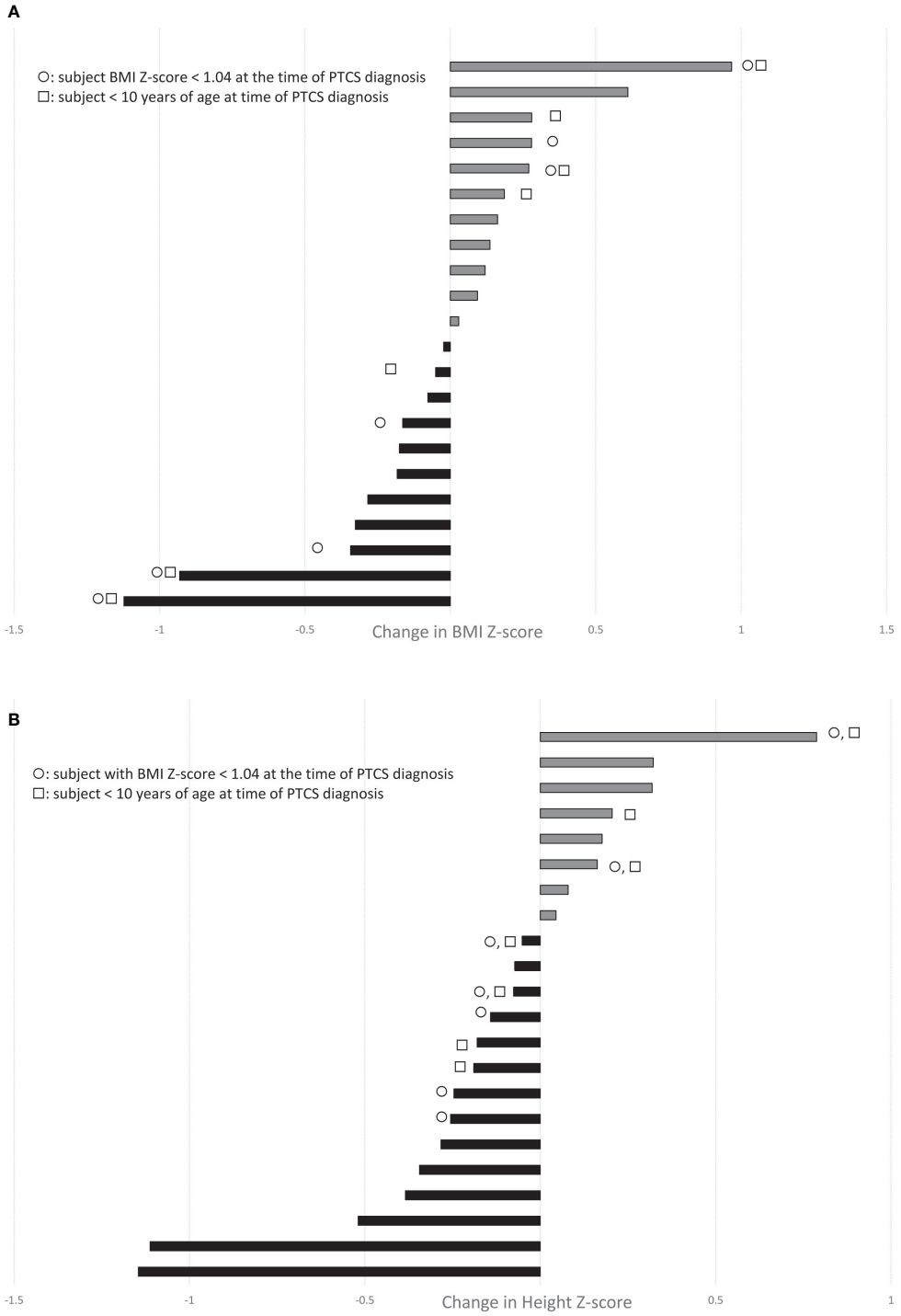

FIGURE 1
Waterfall plots demonstrate the change in **(A)** BMI-Z score and **(B)** Height Z-score during treatment with acetazolamide in our cohort of children with PTCS (range, 1-32 months; n=22 with paired growth data available before and during treatment). Grey bars depict increases, while black bars show decreases. ◯ indicates subjects with BMI Z-score < 1.04 (not overweight or obese) at the time of PTCS diagnosis. □ indicates subjects < 10 yrs of age at PTCS diagnosis.

discontinuing acetazolamide over a range of 6 – 33 months). Qualitative analysis suggests the possible effects of acetazolamide on growth suppression may, in part, be reversible. Six children developed a decrease in height Z-scores during treatment with acetazolamide, and of these, 3 showed at least a partial recovery of height Z-scores after discontinuation of the drug (Figure 2A). Five had a decrease in BMI Z-scores during treatment with acetazolamide (Figure 2B).

Discussion & conclusion

Previous studies on other diseases have suggested that in some susceptible children with other diseases, acetazolamide can suppress growth. If acetazolamide plays a causal role in growth suppression in some children with PTCS, the mechanism is not entirely clear. To our knowledge, the effect of acetazolamide on growth in pediatric PTCS

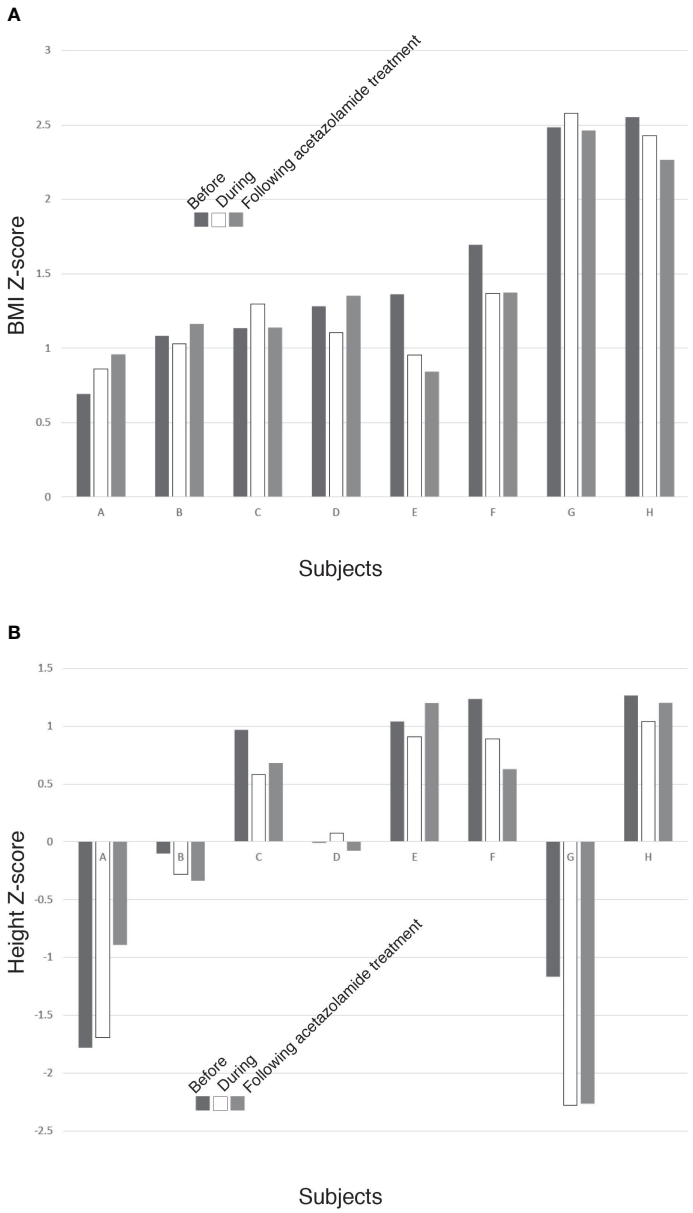

FIGURE 2
Bar graphs showing **(A)** BMI Z-scores & **(B)** Height Z-scores measured before (black bar) during (white bar) and following (grey bar) treatment with acetazolamide in the 8 subjects (A–H) who had those three measurements. In **(A)** 5 children (B, D, E, F, H) had a decrease in BMI Z-scores during treatment with acetazolamide. In **(B)**, 6 children (B, C, E, F, G, H) developed a decrease in height Z-scores during treatment, and of these, 3 (C, E, H) showed at least a partial recovery of height Z-scores after discontinuation of acetazolamide.

has not been evaluated systematically. We found that some children with PTCS developed growth suppression during acetazolamide treatment. There was no obvious relationship to young age or weight. Fortunately, the possible effect of acetazolamide on growth may be reversible after treatment cessation, at least for the treatment durations captured in our review. Future larger prospective studies are required to confirm our findings.

How acetazolamide may lead to growth suppression in this group remains unclear. Prior studies have proposed metabolic acidosis induced by acetazolamide as the mechanism by which growth retardation is induced in children; however, downstream details are unclear, with varied hypotheses including alterations in thyroid hormone homeostasis and blunting of growth hormone secretion (10). *In vitro* studies have illustrated that acetazolamide may decrease lipogenesis in adipose cells, as well as potentiate growth inhibition and induce cell cycle arrest and apoptosis in other model systems (13). Clinically, a handful of studies have demonstrated the use of acetazolamide for weight loss in adults without PTCS. For example, acetazolamide has been used for the management of antipsychotic-associated weight gain, in a manner analogous to the effects seen with topiramate (14, 15). Whether these effects occur in the pediatric population and, the extent to which they depend on the dose and/or duration of acetazolamide therapy is unknown.

The retrospective nature and small sample size are the largest limitations of this study. The majority of patients are scheduled at regular intervals based on practitioner practice (GTL); however, visits to the neuro-ophthalmologist naturally do vary, inducing possible sampling bias for measurement of height and weight. Further prospective studies are needed, with additional recording of dosing and compliance with acetazolamide treatment.

Despite these limitations, our findings suggest that acetazolamide may be associated with growth suppression in some children during the management of pediatric PTCS. Fortunately, in several cases, the growth suppression appears to reverse at least in part once the acetazolamide is stopped. Because of the findings of this study, 1) before starting acetazolamide in children we discuss with parents this potential side effect but also its reversibility, and 2) when papilledema is improving, we might halve the dose of acetazolamide or discontinue it if growth suppression occurs. This study emphasizes the necessity to measure routinely the height and weight of children during and after discontinuation of acetazolamide in the management of pediatric PTCS, and also underscores the need for further prospective study into this potentially deleterious effect of acetazolamide. We are currently designing an multicenter prospective pediatric PTCS study to characterize better the clinical and laboratory features of PTCS in this age group as well as to further our understanding of the disease mechanism in children. In this study we will include an analysis of the side effects of acetazolamide in children with PTCS.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Children's Hospital of Philadelphia Institutional Review Board (IRB)/Ethics Committee. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the institutional requirements.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflict of interest

SR was employed by the company Ophthalmic Plastic & Cosmetic Surgery.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Incidence, risk factors and ophthalmic clinical characteristic of ethambutol-induced optic neuropathy: 7-year experience

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Background: The purpose of this research was to investigate the characteristics, clinical manifestations, incidence, and risk factors in ethambutol-induced optic neuropathy (EON) in the Thai population.

Methods: Patients treated with ethambutol for tuberculosis (TB) were retrospectively identified in the medical record of a tertiary hospital in Thailand from January 2012 to August 2019. Development of EON was determined through review of ophthalmology records. Comparison was made between patients with EON and those without EON to identify possible risk factors. Ophthalmic outcomes were characterized.

Results: Among 4,141 patients who received ethambutol for TB treatment, 1,062 had an ophthalmology encounter, and 20 (0.5% overall, 1.88% with ophthalmology encounters) developed EON. In unadjusted analysis, compared to patients without EON, those with EON had a similar daily dose, but longer duration of ethambutol treatment (P=0.02). They were older (mean 43.74 vs. 58.60 years, P=0.001), more likely to have hypertension (P=0.02) and smoke (p=0.01). There were no differences in gender, body mass index, diabetes, dyslipidemia, HIV infection or glomerular filtration rate. The peripapillary retinal nerve fiber layer, ganglion cell analysis, and vascular density as measured using retinal optical coherence tomography were impacted by EON. In adjusted logistic regression analysis, age greater than 60 (OR = 8.71, p = 0.01) and smoking (OR = 7.06, p = 0.01) were independent risk factors for EON.

Conclusion: In patients treated with ethambutol, the incidence proportion of EON was 0.5% among those with ethambutol administered and 1.88% among those with ethambutol and an eye visit. Potential EON risk factors were age, hypertension, smoking, and duration of ethambutol medication. Smoking has not been associated with EON in prior studies.

KEYWORDS

ethambutol, optic neuropathy, drug toxicity, visual impairment, tuberculosis

1 Introduction

Tuberculosis (TB) has long been a global public health problem with both health and socioeconomic consequences. Thailand is one of the 30 nations with highest prevalence of TB and HIV/TB co-infection (1). Anti-TB drugs are associated with increased survival of tuberculosis patients. However, side effects, including toxicity to the visual system, impact quality of life and can lead to chronic disability.

Ethambutol is a bacteriostatic antibiotic that is used to treat Mycobacterium strains in combination with other medications. Ethambutol-induced optic neuropathy (EON) is one of the most common and devastating side effects (2). Patients with EON present with subacute painless bilateral visual deterioration, typically starting 2-8 months after initiation of ethambutol administration. Common examination findings are bilateral visual acuity decline, central or cecocentral visual field defect, normal optic disc appearance or mild hyperemic swelling in an early stage, evolving to pallor in a chronic stage. The condition may result in permanent visual impairment if cessation of the causative medication is delayed.

There have been several studies on the occurrence and the clinical presentation of EON, but none of them were undertaken in Southeast Asia, where tuberculosis is common (3–7). The purpose of this study was to investigate the incidence, clinical characteristics, and possible risk factors for developing EON in a tertiary care center in Southeast Asia.

2 Materials and methods

This study is a retrospective observational study of patients who received ethambutol for TB treatment seen at Rajavithi Hospital, Bangkok, Thailand from January 2012 to August 2019. The study protocol was approved by the Institutional Ethics Committee of Rajavithi hospital. The study was registered to the Thai Clinical Trials Registry with a registration number of TCTR20220207006.

2.1 Subjects

Patients who received ethambutol for TB standardized treatment regimen which is usually not exceed 25 mg/kg/d at Rajavithi Hospital, Bangkok, Thailand from January 2012 to August 2019 were identified from the hospital database. Subjects were grouped as ethambutol-induced optic neuropathy (EON) and non-EON. Inclusion criteria for EON were ICD-10 code H47 (other disorders of optic nerve and visual pathways) in the hospital database and confirmed as incident EON during the study period by chart review. The patients who received ethambutol during the study period without confirmed EON were classified as control (non-EON). Non-EON patients with an ophthalmology encounter during the study period were classified as controls with eye examination (non-EON with eye encounter). 173 non-EON patients with eye encounters were selected at random for review of ophthalmology records in order to validate the classification of non-EON status. Exclusion criteria for all subjects were incomplete or lost medical record.

2.2 Variable definition

For all subjects, demographic data including age at the time ethambutol treatment was started and gender were collected. Primary target organ of TB infection, total duration and daily dose of ethambutol were extracted from the hospital data base. Body mass index (BMI) at time of starting drug, and history of cigarette smoking were also extracted. Medical history including the presence of other underlying medical conditions such as hypertension, diabetes mellitus, dyslipidemia and HIV infection were noted.

In EON subjects, ophthalmic data, including visual acuity, pattern of visual field defect, color vision, and optic disc abnormalities were extracted from the medical record. The results of optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), using SPECTRALIS® (Heidelberg Engineering, Germany) were recorded when available.

2.3 Statistical analysis

EON incidence proportion (cumulative incidence) was calculated as the proportion newly diagnosed cases of EON during the defined period relative to total number of individuals treated with ethambutol for TB (EON + non-EON) and relative to the total number of individuals treated with ethambutol for TB who had an eye exam during the study period (EON + non-EON with eye encounter). To determine which factors were associated with EON, Chi-square test and Fishers' Exact test were used for categorical variables, t-test for independent samples was used for the comparison of continuous variables. Logistic regression analysis was used to investigate all factors that differed between groups and may be linked to the development of EON. A p-value less than 0.05 was considered statistically significant. The data were analyzed using SPSS version 20.0 (IBM Inc.).

3 Results

3.1 Incidence of ethambutol-induced optic neuropathy (EON)

Twenty (0.5%) of the 4,141 patients who received ethambutol for TB treatment during the study period were diagnosed as EON. Among the 1,062 patients with eye examinations incidence of EON was 1.88%. We randomly examined the medical records of 173 patients receiving ethambutol with eye exam and lacking ICD code H47 and confirmed that none of them were diagnosed with EON (Figure 1). Of the 20 EON patients, twelve patients had primary pulmonary tuberculosis, four had tuberculosis of the spine, one had

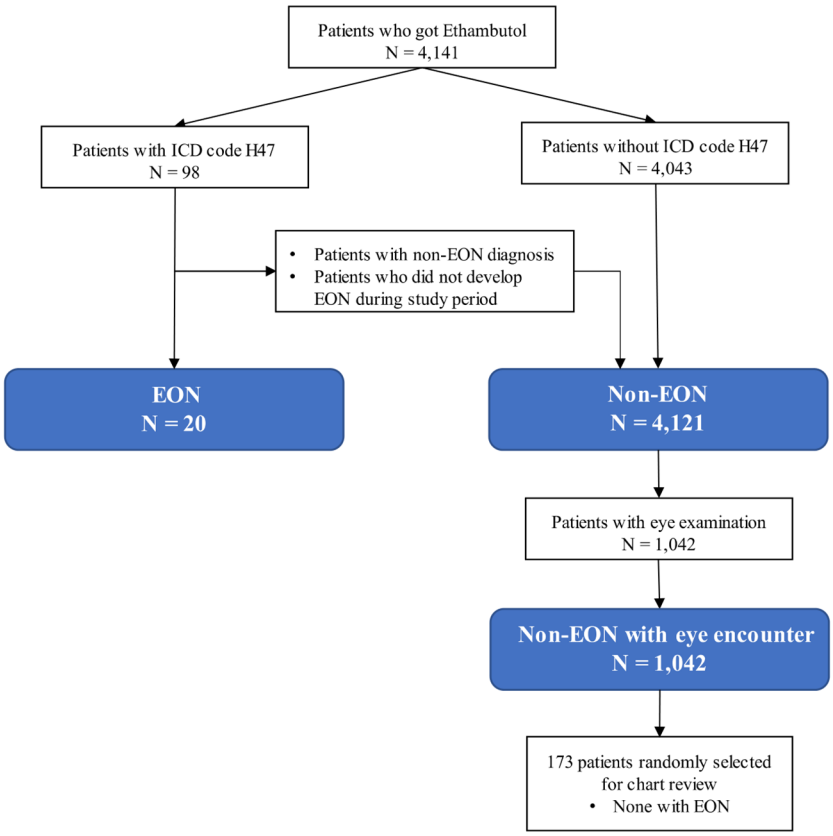

FIGURE 1
Flow diagram of patient selection.

tuberculosis of the knee, one had pleural tuberculosis, one had liver abscess tuberculosis, and one had tuberculosis meningitis (Table 1).

The ages of EON affected patients ranged between 27 and 74 years (mean 58.6 ± 12.0 years); 13 were men and 7 were women. The average BMI was 20.7 ± 2.8 Kg/m^2 (n=16). There were 5 (25%) patients with diabetes mellitus, 7(35%) patients with hypertension, 4(20%) patients with dyslipidemia. There was no HIV patient in the EON affected group. 4(20%) patients had a history of cigarette smoking. The average glomerular filtration rate (GFR) was 87.8 ± 29.5 mL/min. The mean dose and duration of ethambutol were 19.1 ± 3. 9 mg/kg/day and 235.6 ± 122.9 days, respectively (Table 1).

3.2 Unadjusted comparison

In unadjusted analysis, patients with EON were older than those without EON, regardless of comparison group (P = 0.001, t-test). Body weight and BMI were not different between EON and non-EON groups. Smoking was more common in those with EON, regardless of comparison group (P=0.01, fisher exact). When comparing patients with EON to those without EON, hypertension was more common (P =0.02, chi-square). There was no difference between prevalence of diabetes, dyslipidemia, and HIV infection between those with and without EON. GFR did not differ between patients with and without EON (Table 1). There was no difference between the daily ethambutol doses delivered to patients with and without EON, with (P = 0.66, t-test) or without an eye exam (P =0.27, t-test). The duration of ethambutol therapy was longer (P =0.01, t-test) in patients with EON than those without EON (Figure 2).

3.3 Multiple variable models of EON

Age, smoking, hypertension and duration of ethambutol treatment were included in the logistic regression model due to their unadjusted associations with EON status. The incidence of EON was considerably higher in patients over the age of 60, as shown by logistic regression analysis (Table 2). With an odds ratio of 8.71 (P =0.01), patients over the age of 60 had a higher incidence of EON than those under the age of 40. Smoking status also remained independently associated in the adjusted model (OR 7.06, P=0.01). Hypertension was also associated with EON in the adjusted model but did not reach the statistical significance threshold (P=0.14). Duration of ethambutol was not associated with EON after adjusting for other variables (P=0.06).

3.4 Ophthalmic clinical characteristics

All of the EON patients had symptoms of bilateral painless visual loss. Visual acuity ranged from NPL to 20/20 at presentation.

TABLE 1 Characteristics of ethambutol treated patients with and without EON.

	Non-EON (Controls) (n = 4121)	Non-EON (Controls) with eye examination (n = 1042)	EON cases (n = 20)
Gender			
Male, n (%)	2383 (57.8)	571 (55.9)	13 (65)
Female, n (%)	1738 (42.2)	450 (44.1)	7 (35)
Age (years) (mean ± SD)	43.74 ± 16.94	46.37 ± 16.31	58.60 ± 12.01◊
Weight (Kg) (mean ± SD)	61.47 ± 16.85	65.17 ± 18.77	57.50 ± 9.05
BMI (kg/m^2) (mean ± SD)	22.92 ± 5.99	24.07 ± 6.69	20.72 ± 2.82
Smoking, n (%)	204 (4.9)	39 (7.4)	4 (20)†
DM, n (%)	458 (11.1)	274 (26.8)	5 (25)
HTN, n (%)	576 (13.9)	293 (28.7)	7 (35)*
DLP, n (%)	504 (12.2)	302 (29.6)	4 (20)
HIV, n (%)	628 (15.2)	309 (30.2)	2 (10)
GFR (mL/min) (mean ± SD)	99.21 ± 28.13	93.84± 29.49	87.81 ± 29.50
EMB Dose(mg/kg/day) (mean ± SD)	15.25 ± 3.54	14.49± 3.65	19.12 ± 3.89
Duration of EMB prescription (days) (mean ± SD)	106.94 ± 225.81	159.96 ± 306.89	235.60 ± 122.86◊

* P-value < 0.05 versus each control group in chi-square test, † P-value < 0.05 versus each control group in fisher exact test, ◊ P-value < 0.05 versus each control group in t-test.
EON, ethambutol optic neuropathy; BMI, Body Mass Index; DM, Diabetes Mellitus; HTN, Hypertension; DLP, Dyslipidemia; HIV, Human immunodeficiency virus; GFR, Glomerular filtration rate; EMB, ethambutol.

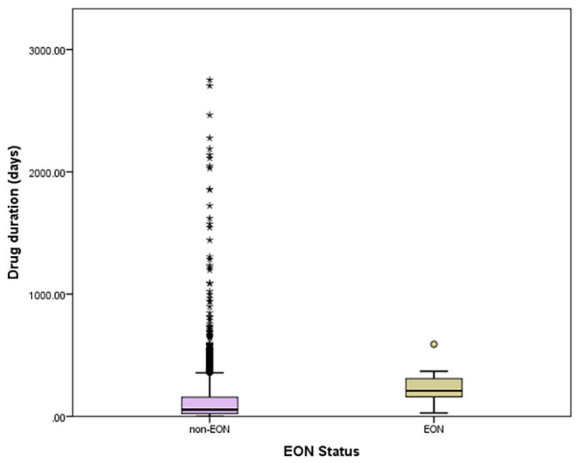

FIGURE 2
Distribution of ethambutol treatment duration according to EON status (all patients). Box boundaries are 25%ile and 75%ile, error bars are 5%ile and 95%ile, other symbols are cases between 95%ile and 100%ile.

2 patients (10%) had only a slight decrease in visual acuity but showed abnormalities in their visual fields.10 patients who were able to take a color test were found to have a color deficiency. The most common visual field defects were central or cecocentral scotomas [3 patients (15%)] and bitemporal scotomas [2 patients (10%)].

The duration of ophthalmic follow-up following EON diagnosis at eye appointment ranged from 2 to 83 months (21.7± 25.2). After stopping ethambutol, the visual function of 12 patients (60%) improved by at least 2 lines on the Snellen chart, with a mean recovery time of 6.9 months. There were no differences in demographics, past medical history, smoking, or ethambutol dosing between patients who did and did not recover. Follow up time in non-recovery patients was shorter than for patients with recovery (mean 7.7 months vs. 33.21, P=0.02).

Ophthalmic imaging was available in 9 EON cases. These showed a decrease in the thickness of the peripapillary retinal nerve fiber layer (pRNFL) and macular ganglion cell layer (GCL),

TABLE 2 Logistic regression analysis of the factors for Ethambutol-induced Optic neuropathy.

	Unadjusted OR (95%CI) p-value	Adjusted OR (95%CI) p-value
Age group < 40 years	Ref	Ref
40-60 years	4.92 (1.02-23.71) 0.05	1.75 (0.28-10.84) 0.55
>60 years	14.23 (3.15-64.36) 0.001	8.71 (1.65-45.93) 0.01
Smoking	5.20 (1.55-17.43) 0.007	7.06 (2.00-24.87) 0.01
Hypertension	3.31 (1.32-8.34) 0.01	2.39 (0.65-8.80) 0.14
Duration of Ethambutol	1.01 (1.00-1.02) 0.03	1.00 (0.98-1.03) 0.06

with the latter being more pronounced. In 2 chronic EON patients, characterized by pallor of the disc, OCTA revealed a loss of vessel density in macula whole area (6x6 mm) in both superficial and deep layers. Imaging follow-up was available in 3 cases and revealed minimal progression of pRNFL and GCL loss after ethambutol discontinuation. 2 cases with profound ganglion cell thinning at time of diagnosis, had visual function recovery after ethambutol discontinuation (Figure 3).

Discussion

At a tertiary care medical center in Thailand the incidence of ethambutol optic neuropathy from 2012-2019 was 0.5% among all patients who received ethambutol for TB and 1.88% among patients who received ethambutol for TB with eye examination. In comparison, a recent Taiwanese study reported a 1.29% incidence of EON (8), while earlier studies reported an incidence of around 1% (6) (Table 3). Our overall incidence may be an underestimate due to missing hospital records, undetected diagnoses from other hospitals, or undiagnosed disease.

We found older age to be associated with EON, which is consistent with prior reports (5, 6, 9–11). A recent study by Chen HY, et al. in a Taiwanese population reported that the majority of EON patients are over the age of 65, which is consistent with our findings (4). They hypothesized that age was an independent risk factor for EON mediated by renal function decline (6, 12). Although it is known that renal tubular function declines with age, the aging effect of ethambutol clearance is unknown (12). We also found a lower GFR in the EON group, but it did not reach statistical significance.

Hypertension and smoking were associated with EON in our study. Chen HY et al. study also found that hypertension was associated with EON and hypothesized that the effect was mediated through reduced renal function (4). Smoking is a potential risk factor that has not been reported in association with EON (Table 3). However, there is literature supporting smoking as a risk factor for TB infection, increasing the risk of recurrent TB, and impairing response to disease treatment (13). As a result, we hypothesize that smoking could increase the risk of EON mediated by more severe TB infection perhaps impacting drug regimen in patients who smoke. Another possibility is the adverse effect of smoking on mitochondrial function, which has been proposed as the mechanism for worsening Leber's hereditary optic neuropathy (14). This mechanism could both increase the risk of developing EON and worsen the prognosis of EON.

According to a previous meta-analysis (6), duration and dose of ethambutol were positively related to the risk of EON. In our study, the ethambutol duration was longer in those with EON, though this association did not persist in adjusted models. While the dose in the EON group was higher than in the non-EON group, the difference did not reach statistical significance. This may be because the prescribed ethambutol regimen (15-25 mg/kg/d) was standardized to reduce the risk of EON (15, 16). We hypothesized that because of this standard dosing regimen, duration, rather than higher daily doses of ethambutol, drive total exposure.

The ophthalmic EON characteristics in our study were similar to those in previous studies. Patients with EON typically present with symmetrical bilateral painless visual loss. The most common visual field defects were central or cecocentral scotoma and bitemporal scotoma. We discovered that in 60% of cases, visual function recovered. Chamberlain PD, et al. study's found that patients' recovery rates ranged from 20% to 80%, which is consistent with our findings (3).

There are some limitations that should be mentioned. First, the data of the patients' diagnosis as EON was initially identified using ophthalmology clinicians *via* ICD-10 coding, which could miss cases due to coding errors or not having an eye exam. Second, because this was a retrospective study, selection bias is likely. Third, our sample size is limited, because the computer-based diagnosis was only available at our institution for the 7 years studied. Fourth, because some clinical data, such as special ophthalmic imaging values, were not collected from all EON patients, we were unable to perform a comparative analysis. Fifth, Thailand's standard treatment for tuberculosis during the study perior was multi-drug therapy. In this study, ethambutol optic neuropathy was diagnosed clinically, imaging was used to rule out other causes, and the patients' vision did not worsen after ethambutol was

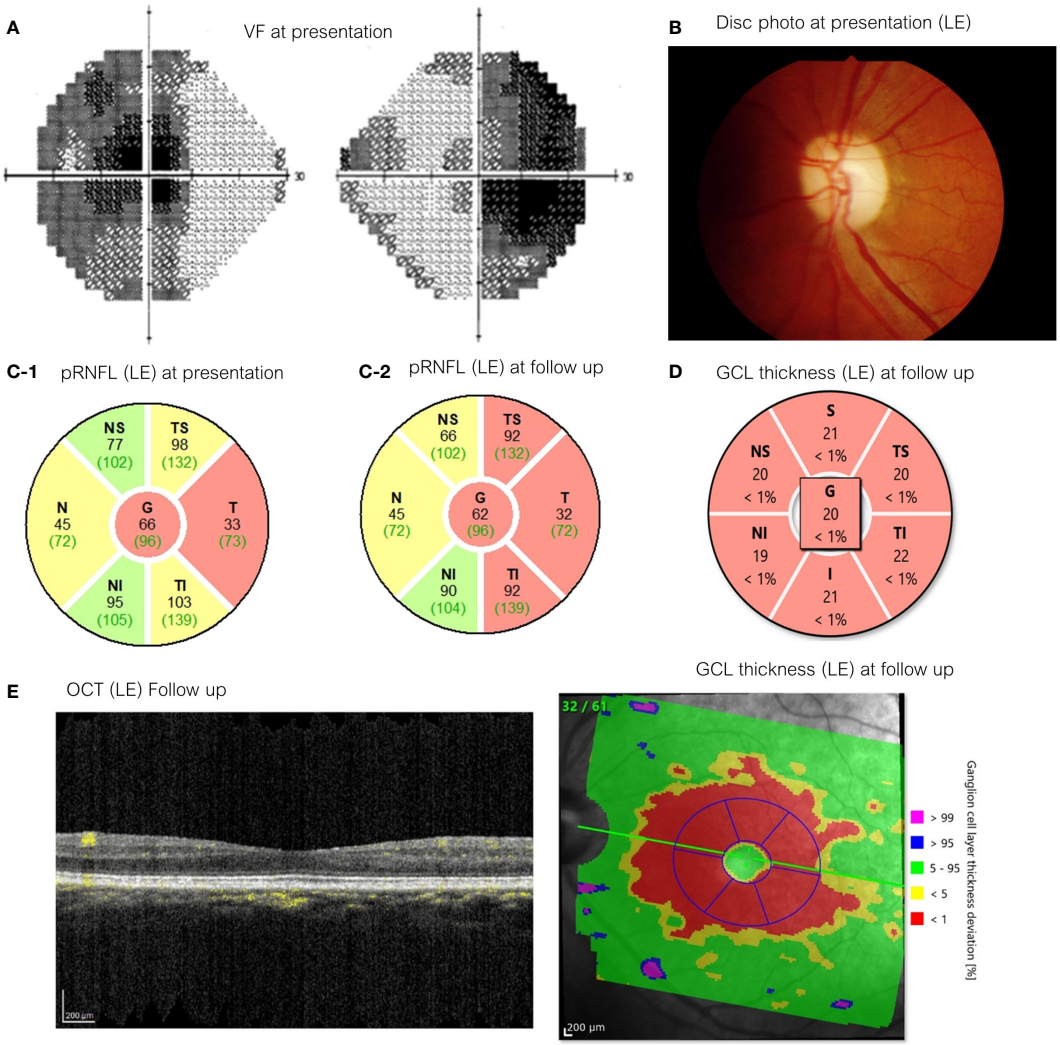

FIGURE 3
A 54-year-old woman with spine tuberculosis examined after 6 months of EMB medication (presentation) with best-corrected visual acuity 20/800 in the right eye and CF2' in the left eye and 4 years after drug cessation (follow up) with VA 20/40 in both eyes. **(A)** Visual field testing showed the presence of Bitemporal hemianopia (presentation) **(B)** Optic disc appearances on her left eye showed mild temporal pallor (presentation). **(C)** pRNFL thickness left eye [C-1: presentation (first visit), C-2: follow up]. **(D)** GCL thickness of left eye (follow up). **(E)** OCT appearance of her left eye (follow up). EMB, ethambutol; CF, Counting fingers; pRNFL, peripapillary retinal nerve fiber layer; GCL, ganglion cell layer; OCT, Optical coherence tomography.

TABLE 3 Table comparing the literature on ethambutol optic neuropathy.

First Author (year)	Country	Study design	Participants	Study time (y)	Incidence Proportion % (cumulative incidence), (incident cases/cohort size)	Factors associated with EON	Visual outcomes
Yang (2016) (3)	Korea	Retrospective	480 non-HIV TB on EMB-containing multidrug regimens	6	0.70% (3/480)	- Age	3 cases presented with EON. Retinal nerve fiber layer thinning in 2 cases
Chen (2012) (4)	Taiwan	Retrospective	11,753 subjects who were dispensed EMB	8	2% (231/11,753)	- Age - Hypertension - Renal diseases	not reported

(Continued)

TABLE 3 Continued

First Author (year)	Country	Study design	Participants	Study time (y)	Incidence Proportion % (cumulative incidence), (incident cases/cohort size)	Factors associated with EON	Visual outcomes
Lee (2008) (5)	Korea	Retrospective	857 patients who started ethambutol treatment for TB infection	2	1.50% (13/857)	- Renal dysfunction - Daily dose of ethambutol	Visual function after discontinuation of ethambutol is reversible in only a minority of patients.
Talbert (2010) (6)	USA	Case series and Meta-analysis	70 cases EON (16 + 54 review)	8	not reported	- Age - Renal dysfunction - Ethambutol dose - Ethambutol duration	not reported
Ezer (2013) (7)	Canada	Systematic review	19 studies before 2011	46	2.02% (102/5042)	No relevant significant factors were found.	not reported
Chen (2015) (8)	Taiwan	Retrospective	4803 newly diagnosed tuberculosis cases	10	1.29% (62/4803)	not reported	No factors associated with visual recovery.

discontinued. However, we cannot rule out other potential causes of optic neuropathy.

In conclusion, the incidence proportion (cumulative incidence) of EON in patients treated with Ethambutol was 0.5%-1.88% depending on the comparison group used. Age, hypertension, smoking, and the duration of ethambutol treatment were associated with EON in unadjusted analysis. Logistic regression showed age greater than 60 and smoking to persist as independent associations after adjustment for other covariates. Further study is needed to confirm smoking as a risk factor and consideration should be given to addressing this potentially treatable risk factor.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

PC, SS, and PR contributed to conception and design of the study. AW organized the database. PC and AW performed the statistical analysis. PC and AW wrote the first draft of the manuscript. PC, PR, SA, and HM wrote sections of the manuscript. HM revised the manuscript as the most recent submission version. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Case Report: Successful treatment of external beam radiation-induced optic papillopathy with intravitreal anti-VEGF

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Three cases of optic disc edema arising from radiation optic neuropathy isolated to the intra-ocular optic nerve following external beam radiation for head and neck squamous cell carcinoma are presented. A literature review of the etiology, presentation, and treatment is included for discussion, along with proposed diagnostic criteria.

KEYWORDS

radiation, optic neuropathy, optic papillopathy, anti-VEGF (vascular endothelial growth factor), intravitreal (IVT) drug, intravitreal bevacizumab (IVB; Avastin), bevacizumab (Avastin), optic disk edema

Introduction

Radiation toxicity to the optic nerve is a known and feared complication of therapeutic radiation indicated for head and neck tumors as well as orbital and CNS tumors (1). Radiation-induced optic neuropathy is more commonly encountered with CNS radiation, with a predilection for the intracranial segment of the optic nerve (1). However, toxicity can affect the intraocular segment of the optic nerve, which is most commonly associated with radiation therapy for intraocular tumors. Various terms have been used for radiation optic neuropathy involving the intraocular optic nerve. It is often termed simply radiation optic neuropathy, for example when discussing the complication of choroidal melanoma, it is often referred to simply as radiation optic neuropathy, but it has also been referred to as anterior radiation optic neuropathy. However, this term is not specific enough to rule out retrobulbar extension, and, therefore, the term radiation-induced optic papillopathy (RIOP) is used in this manuscript. There is limited information in the literature about the visual outcomes and treatment of RIOP associated with the treatment of non-ocular tumors. This paper reports three cases to provide further information on presentation and treatment.

Case series

Case #1

A woman in her early 80s presented with a 1-month history of blurred vision in the right eye. Thirty-nine months prior to her initial presentation she was treated for cutaneous squamous cell carcinoma (SqCCa) of the periorbita, which was deemed unresectable, and was treated with a total of 72 Gy of intensity-modulated (fractionated) external beam radiation (IMRT). Examination of the right eye showed visual acuity of 20/30, color vision of 12/14 Ishihara plates, relative afferent pupillary defect (RAPD) of < 0.3 log-units, and normal ocular motility and alignment. Fundus examination of the right eye showed a red hemorrhage within the optic disc from 3 to 7 o'clock, spilling over the disc rim, and which was associated with mild inferior disc edema, and a remote retinal blot hemorrhage at 6 o'clock. The left eye was normal. Automated visual field (AVF) testing showed faint superior arcuate scotoma (Figure 1); an optical coherence tomography (OCT) cube scan, centered on the optic disc, demonstrated nasal and inferior thickening with cystoid changes and intraretinal hyperreflective foci (Figure 2). Red-free photos highlighted the hemorrhage within the optic disc; fluorescein angiography showed blockage from the hemorrhage and telangiectatic vessels on the optic disc, with diffuse disc staining and profuse fluorescein dye leakage from the optic disc nasally and inferiorly (Figure 3). MRI of the orbits with and without contrast showed possible trace optic disc elevation but no retrobulbar enhancement.

The patient was diagnosed with RIOP and was treated with intravitreal bevacizumab (IVB). The optic disc edema resolved after four doses of monthly IVB. The patient was treated with a treat-and-extend protocol for a total of eight doses and followed up for 13 months after her last injection. At the last follow-up, visual acuity was 20/25, AVF testing showed a superior arcuate defect with a relatively stable mean deviation of –4 dB with a baseline value of –2.1 dB, and OCT showed that the thickness of the peripapillary retinal nerve fiber layer (RNFL) had improved from the baseline value of 118 to 86 µm (Figure 2).

Case #2

A woman in her early 60s presented with a 5-month history of blurred vision in the right eye. Fifty months prior, she had completed IMRT for SqCCa of the right lacrimal sac, receiving a total dose of 72 Gy, combined with chemotherapy. Her SqCCa was complicated by metastases to the right parotid gland and cervical

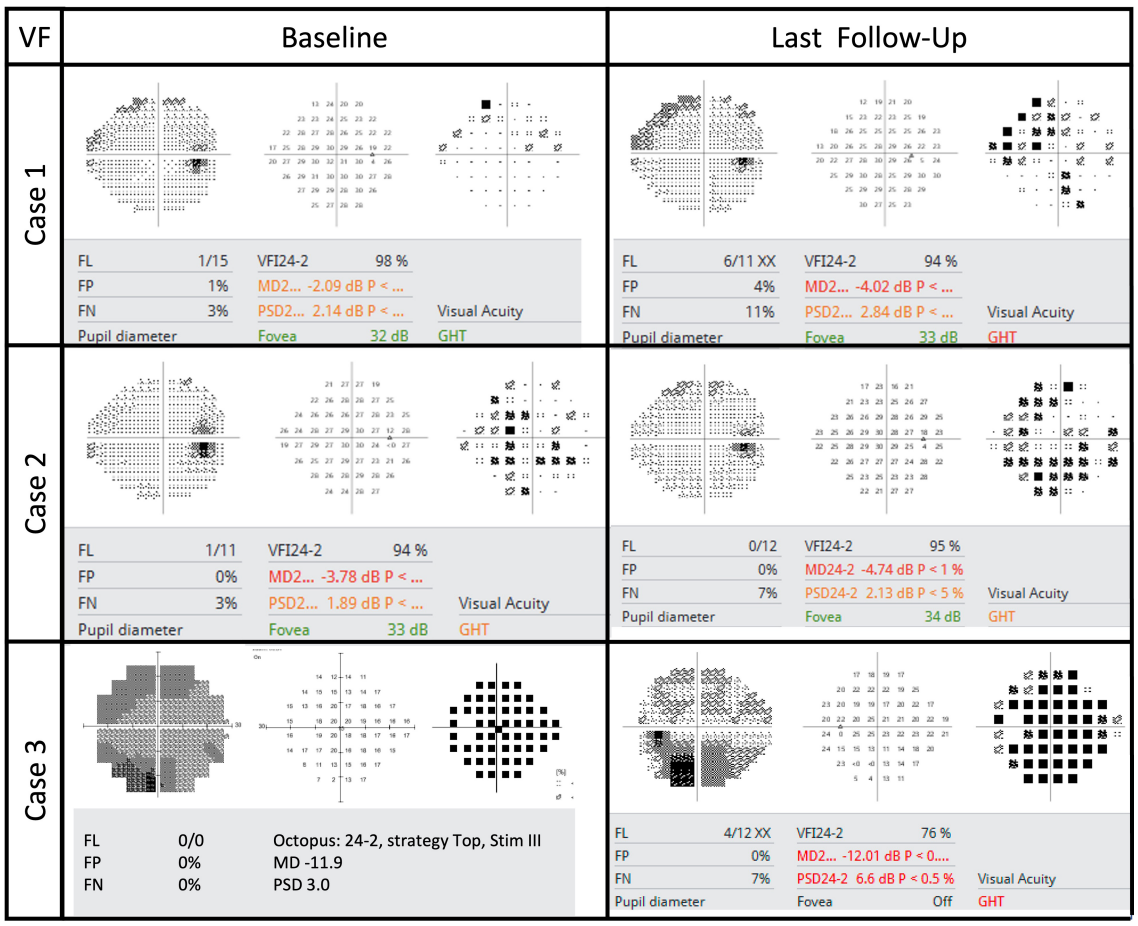

FIGURE 1
Automated visual fields at baseline and final follow-up.

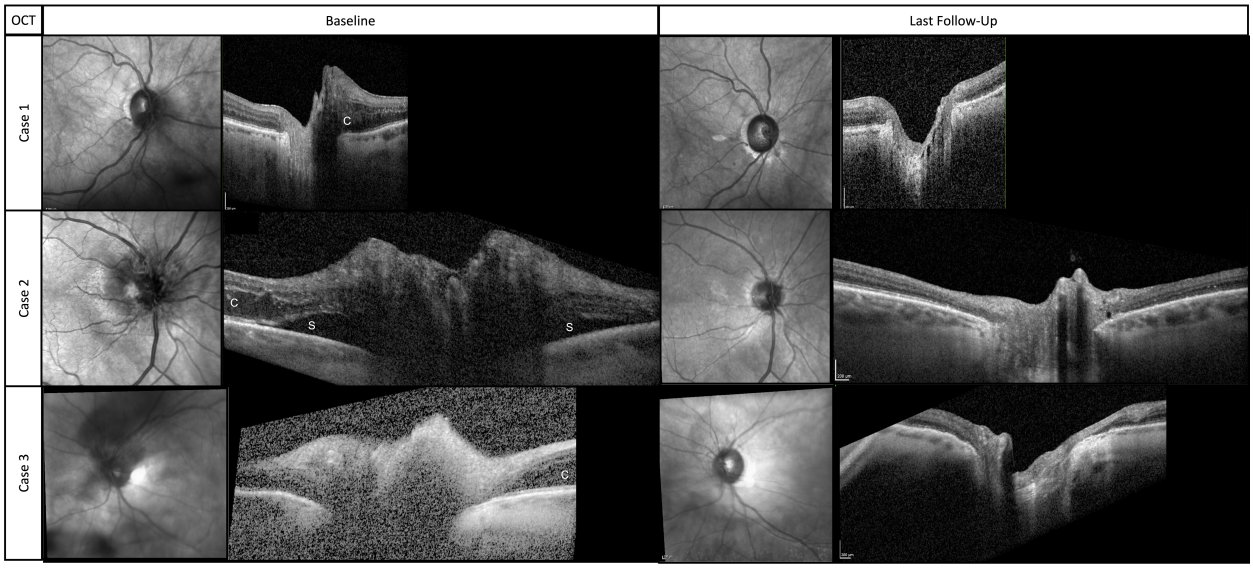

FIGURE 2
Near-infrared images and associated cross-sectional OCT scans through the optic disc at baseline and final follow-up. (c) indicates cystoid changes from intraretinal fluid. (s) indicates subretinal fluid.

lymph nodes, which were treated with 67 Gy. Examination of the right eye demonstrated visual acuity of 20/25, color vision of 12/14 Ishihara plates, no detectable RAPD with a 0.3 log-unit neutral density filter, and normal ocular motility and alignment. Fundus examination of the right eye revealed 360 degrees of optic disc edema, worst superiorly, with telangiectatic blood vessels, a tiny cotton wool spot, a few nerve fiber layer hemorrhages, and exudates and thickening in the nasal macula. AVF testing revealed an enlarged blind spot and general depression with a mean deviation of –3.8 dB, and OCT demonstrated 360 degrees of peripapillary subretinal fluid and nasal cystoid macular edema (Figure 2). MRI of the orbits with and without contrast was negative for optic nerve enhancement.

The patient was diagnosed with RIOP and was treated with IVB. The optic disc edema resolved after six doses of monthly IVB. The patient was treated with a treat-and-extend protocol for a total of nine doses and followed up for 12 months after her last injection. At the last follow-up, visual acuity was 20/25, AVF testing showed a superior arcuate defect with a relatively stable mean deviation of –4.7 dB with a baseline level of –3.8 dB (Figure 1), and OCT showed that the thickness of the RNFL had improved from 246 µm at baseline to 75 µm (Figure 2).

Case #3

A woman in her early 60s presented with a 1-month of blurred vision in the left eye with new floaters. Thirty months prior, she had completed IMRT combined with chemotherapy for perineural invasion by cutaneous SqCCa involving the left side of her face and the trigeminal nerve for a total dose of 72 Gy. SqCCa had initially been diagnosed 5 years prior, at which time she underwent Mohs surgery; perineural invasion was initially detected 3 years prior and was being treated with cemiplimab (anti-programmed cell death receptor 1 monoclonal antibody). Examination of the left eye demonstrated visual acuity of 20/100; color vision of 14/14 Ishihara plates; 0.3 log-unit RAPD; ptosis and 25%–50% limitation of elevation, adduction, and depression; telangiectatic skin changes over the brow and upper eyelid; 360 degrees of mild corneal neovascularization with guttae and central haze; and mild cataracts. Dilated fundus examination revealed a hazy view, mild vitreous hemorrhage extending from the optic disc, and hemorrhage within the nerve fiber layer extending from the optic disc. Ancillary testing included AVF testing, which showed generalized depression with a mild inferior scotoma on pattern deviation and a mean deviation of –11.9 dB (Figure 1); an OCT cube scan centered on the optic disc was notable for superonasal cystoid changes extending into the macula and mild diffuse thickening of the peripapillary RNFL (Figure 2). MRI of the skull base protocol with and without contrast demonstrated no retrobulbar optic nerve infiltration.

The patient was diagnosed with RIOP and was treated with IVB. The optic disc edema resolved after four doses of monthly IVB. The patient was treated with a treat-and-extend protocol for a total of seven doses, and the last follow-up was 30 months after her last injection. At the final follow-up, visual acuity was 20/60, AVF testing showed general depression and mild inferior scotoma, the mean deviation was stable at –12 dB, with a baseline of –11.9 dB (Figure 1), and the OCT RNFL thickness measurement improved from 118 µm at baseline to 76 µm (Figure 2).

Table 1 provides details of all three cases. Ages are reported in decade form to protect the patients' privacy.

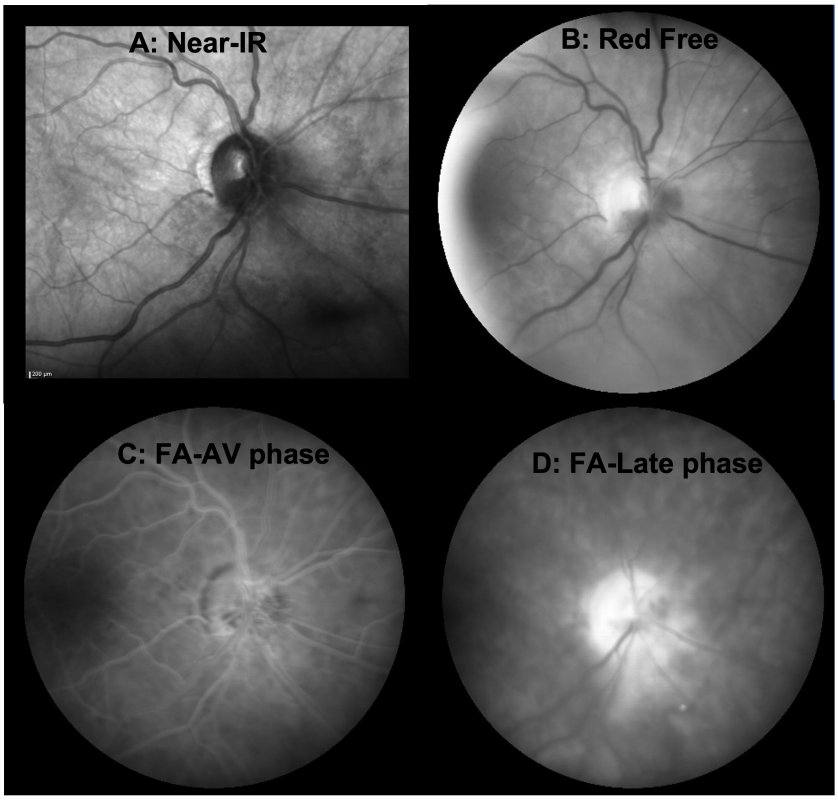

FIGURE 3
En face imaging of the acute phase of RIOP from case 1. **(A)** Near-infrared image acquired during OCT scanning of the optic nerve showing clustered pinpoint hyporeflectivity surrounding the optic disc from 12 to 8 o'clock, corresponding to cystoid changes on cross-sectional OCT but no frank optic disc edema. **(B)** Red-free photograph highlighting the hemorrhage within the optic disc from 2 to 8 o'clock. **(C)** Fluorescein angiogram in the arteriovenous phase, which shows hypofluorescence due to blockage from the hemorrhage within the optic disc along with telangiectatic vessels on the optic disc but no neovascularization. **(D)** Fluorescein angiogram in the late stage demonstrating diffuse optic disc hyperfluorescence from staining, some inferonasal leakage, and some residual blocking from hemorrhage.

Discussion

Little is published about the treatment of radiation-induced optic neuropathy limited to the intraocular segment of the optic nerve (optic papillopathy, RIOP). The most common clinical scenario of RIOP encountered is following brachytherapy for choroidal melanoma, partly due to the frequency of choroidal melanoma, the high-dose exposure in proximity to the optic nerve, and the fact that patients getting frequent eye exams while monitoring for tumor progression and complications such as radiation retinopathy. Head and neck SqCCa, particularly if it involves periorbital structures such as cutaneous lesions and those originating in the sinuses and nasopharynx, as seen in all three cases reported in this series, is also particularly high risk due to the high total dose required for local tumor control in combination with proximity to the optic nerves, resulting in a high maximum point dose to the optic nerves (1).

Traditionally, RIOP associated with brachytherapy has been treated by retinal specialists using methods similar to radiation retinopathy with intravitreal anti-VEGF and intravitreal steroids, but without evidence from randomized controlled trials (RCTs) (2). Eckstein et al., in 2019, called into question the long-term benefits of intravitreal injections in the setting of proton therapy for choroidal melanoma; however, these patients are treated with a high dose per fraction (14–15 Gy equivalent), which is much higher than the standard dose per fraction. This results in increased toxicity to both the macula and the optic nerve, compared with treatment for head and neck and CNS cancers, which may account for the poorer visual prognosis (1, 3). Systemic (intravenous as well as intra-arterial) bevacizumab has been used to treat CNS radiation toxicity, including in an RCT of both saline placebo and steroids and a case series in patients who have failed steroids, anticoagulation, and hyperbaric oxygen (4–7). Systemic bevacizumab for the treatment of retrobulbar radiation-induced optic neuropathy has been studied in multiple case series, but none has included an RCT (1). Intravitreal treatment for RIOP was selected in these case series due to the ability to deliver the medication to the site of injury and limit systemic exposure and toxicities, as compared with systemic administration.

The optimal treatment protocol for RIOP is also not clear. In the case of radiation retinopathy, some authors recommend continuous treatment for radiation retinopathy on the basis that, although presenting manifestations will resolve with treatment, late findings of vasculopathy including microaneurysms and capillary non-perfusion can still develop (8). Other retinal vascular diseases, such as diabetes and retinal vein occlusions, can be treated

TABLE 1 Radiation-induced optic papillopathy case series.

	Case 1	Case 2	Case 3
Cancer diagnosis	Cutaneous facial SqCCa	Lacrimal sac SqCCa	Cutaneous facial SqCCa with perineural invasion
Total radiation dose	72 Gy	72 Gy	72 Gy
Decade of age at diagnosis of optic neuropathy (years)	80s	60s	60s
Time from radiation to optic neuropathy diagnosis (months)	39	50	30
Vasculopathic risk factors	Hypertension	Hypertension. dyslipidemia	None
Other ocular conditions	PCIOL, OAGS, DBN, DCR	PCIOL, dry eyes	Cataract, 3NP, recurrent HSV keratitis, exposure keratopathy
Visual acuity at diagnosis	20/30	20/25	20/100
Color vision at diagnosis	12/14	12/14	14/14
Visual field at diagnosis (dB)	MD −2.1; mild superior arcuate	MD −3.8; enlarged blind spot, general depression	MD −12; general depression
Optic disc appearance at diagnosis	Inferior edema	Diffuse edema	Superior edema, overlying VH
OCT RNFL thickness at diagnosis (microns)	118, infranasal cystoid changes	246, peripapillary subretinal fluid with cystoid changes extending into macula	118, cystoid changes extending into macula
Treatment course	TAE, eight doses of IVB	TAE, nine doses of IVB	TAE, seven doses of IVB
Time to optic disc edema resolution post first injection (months)	4	6	5
Duration of follow-up after last anti-VEGF (months)	13	12	30
Visual acuity at last follow-up	20/25	20/25	20/60
Visual field at last follow-up (dB)	MD −4; superior arcuate	MD −4.7; faint inferior arcuate	MD −12.1; general depression
OCT RNFL thickness at last follow-up (μm)	86, normal	75, superonasal thinning	76, superior broad thinning, inferior focal thinning

SqCCa, cutaneous squamous cell carcinoma; PCIOL, posterior chamber intraocular lens; OAGS, open-angle glaucoma suspect; DBN, downbeat nystagmus; DCR, dacryocystorhinostomy; 3NP, third nerve palsy; VH, vitreous hemorrhage; HSV, herpes simplex virus; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; MD, mean deviation; TAE, treat and extend; IVB, intravitreal bevacizumab; VEGF, vascular endothelial growth factor.

successfully with an as-needed regimen, starting with monthly intravitreal injections and, once intraretinal and subretinal fluid have resolved, pausing treatments, resuming only in the event of vision-threatening recurrence of exudation (9). A third option, known as treat and extend, similarly begins with monthly injections, but once fluid has resolved the treatments are spread out, at 2-week intervals (unless exudation recurs, at which point the interval is shortened), typically for 12–14 weeks, at which time treatment can be continued for maintenance or paused and the patient monitored for recurrence (10). The as-needed treatment may result in fewer treatments; however, if exudation recurs, the interval between treatments could be longer, and, therefore, risk more severe exudation, which may cause an irreversible decline in visual acuity. Treat and extend was recommended for the patients reported in this series, as recurrent optic disc edema may result in compartment syndrome and permanent optic nerve damage and vision loss; in addition, it was felt that RIOP is likely an ischemic disease and a longer treatment course may help allow disease control during the vascular remodeling process.

Short-term results of intravitreal steroids for RIOP have been described by the Shields group from nine patients secondary to plaque brachytherapy for choroidal melanoma (11). The mean time from radiation to RIOP was 18 months, ranging from 6 to 33 months. Eight patients were treated with a single injection and one patient received two injections 6 months apart. The optic disc edema resolved at a mean of 4 months after injection (ranging from 1 to 11 months). Shields et al. reported that 78% of patients had improved or stabilized vision (five out of nine improved).

Results of IVB for RIOP have been described by Finger and Chin from 14 patients secondary to plaque brachytherapy for choroidal melanoma (12). The mean time from radiation to RIOP was 42 months, ranging from 11 to 114 months. The mean number of injections was 11, ranging from 2 to 21, given every 6–8 weeks, over a mean period of 22 months. The majority (11/14) of patients

received continuous treatment. Treatment was stopped only if the patient died or was non-adherent, or if treatment was futile (no improvement from baseline in ability to count fingers). Optic discs were stabilized in a mean of 5 months. Vision was stabilized or improved in 64% of patients (7/14 improved).

Roelofs et al. investigated a combination of bevacizumab and triamcinolone for RIOP in nine patients secondary to plaque brachytherapy for choroidal melanoma (13). The mean time from radiation to RIOP was 17 months, ranging from 8 to 28 months. The mean time to the resolution of the disc edema was 7 months. The authors divided their patients into those with acute vision loss ($n = 4$) and those without ($n = 5$). Improvement was experienced by 100% of the acute vision loss group, and 80% of those without vision loss showed stabilization (although in two of these cases, stabilization was at visual acuity of 20/400 and hands motion at baseline).

There has been a single case report of the use of intravitreal bevacizumab for RIOP following external beam radiation therapy for head and neck cancer (14). The patient developed vision loss 6 years after radiation, with visual acuity reduced to 20/50 with a combination of RIOP and maculopathy with subretinal fluid. Following treatment with a single intravitreal injection of bevacizumab, visual acuity improved to 20/20 within 2 weeks.

Clear diagnostic criteria do not exist in the literature. Proposed diagnostic criteria based on the literature and the cases within this report are as follows: (1) optic disc edema in the affected eye with hemorrhages involving the nerve fiber tissue within the margin of the optic disc; (2) evidence of optic nerve dysfunction (i.e., reduced visual acuity or color vision, or nerve fiber bundle-type visual field defect); (3) no signs of retrobulbar optic nerve involvement on MRI (no enhancement or diffusion-weighted imaging signal changes); (4) no signs of tumor infiltration or compression; (5) completion of radiation treatment at least 6 months prior with involvement of the optic disc in the field of radiation; and (6) no alternative cause, such as retinal vascular occlusion, infectious optic papillitis/neuroretinitis, optic nerve infiltration/compression, or inflammatory optic neuritis.

Radiation retinopathy may be used in conjunction with RIOP. It is important to distinguish RIOP from retrobulbar optic nerve disease because intravitreal treatment is unlikely to provide the necessary therapeutic doses to the retrobulbar optic nerve, which could result in undertreatment and progressive optic neuropathy with progressive vision loss. Therefore, MRI of the orbits with and without contrast with fat suppression is recommended.

RIOP may be difficult to distinguish from non-arteritic anterior ischemic optic neuropathy (NAION), and, in truth, there is probably a non-vasculitis ischemic component to RIOP. The two features that best distinguish NAION from RIOP are (1) the atypical hemorrhages within the optic disc and (2) the peripapillary exudation, both of which are out of proportion to the extent of the optic disc edema and were demonstrated in all three of these cases. Persistent optic disc edema may be seen past the typical time expected in NAION, as demonstrated in case 2. This patient had optic disc edema 5 months after symptom onset. All patients had optic disc edema for an additional 3–5 months once treatment was initiated (the patient in case 2 had a total duration of optic disc edema of 10 months). In addition, the visual field defects seen in these three cases are not typical for NAION, and the RAPDs were all very small. It is possible that patients with RIOP may present with more severe vision loss that may more closely mimic NAION or even arteritic disease. Oncology patients are often immunosuppressed, and, therefore, at increased risk of atypical infections; with newer checkpoint inhibitors they may develop atypical optic neuritis, which should be included in the differential diagnosis (15, 16).

The exact etiology of RIOP, or any manifestation of radiation-induced optic neuropathy, is not fully understood. Among the proposed etiologies are direct neural injury, including apoptosis induction, oligodendrocyte injury, and vascular injury with a combination of ischemia and vascular incompetence leading to leakage (1, 7, 17). A vascular etiology is particularly supported when relying on radiation retinopathy as a model for neuropathy in which capillary non-perfusion, reduced retinal blood flow, increased oxygen saturation, and vascular leakage can be demonstrated *in vivo*. (18, 19)

Certainly, there are limitations to this study, including the small numbers and lack of a control group. There are no historical controls or natural history studies of patients with RIOP due to treatment of non-ocular tumors with which to compare our findings. A larger series with longer-term follow-up from multiple institutions would be of benefit, and, in an ideal world, an RCT comparing placebo and intravitreal steroids would be of greatest benefit; however, given the rarity of this condition, this would prove quite challenging. In addition, studies are needed to better elucidate risk factors and ideal surveillance regimens.

In conclusion, RIOP is a rare complication of therapeutic radiation for the head and neck as well as CNS tumors marked by atypical optic disc edema and hemorrhage with peripapillary exudation without retrobulbar involvement. Successful treatment with IVB is possible, and early recognition is key, as the final visual outcome likely depends on vision at the time of treatment initiation. Optimal treatment protocols have not been developed, and further research is required, likely necessitating multicenter studies owing to the rarity of the disease.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethics review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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New advancements in the management of Neuromyelitis Optica spectrum disease: literature review

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Neuromyelitis Optica spectrum disorder (NMOSD) is a relapsing autoimmune disease of the central nervous system (CNS) where aquaporin-4 water channels are the antigenic target of the disease. The spectrum of the disease involves regions of the CNS where the water channel is widely expressed including the spinal cord, the optic nerve, dorsal medulla, brainstem, and thalamus/hypothalamus. Management of NMOSD includes acute as well as long term treatment. Acute symptoms are typically treated with intravenous corticosteroids and/or plasma exchange while long-term treatment involves the use of immunosuppression/immune modulation. The year 2019 is thought to be the "year of the NMOSD" as three new medications became available for this devastating disease. In this review, FDA approved NMOSD medications are discussed.

KEYWORDS

Neuromyelitis Optica spectrum disorder, Eculizumab, Satralizumab, Inebilizumab, therapy

Introduction

Neuromyelitis Optica spectrum disorder (NMOSD) is an autoimmune relapsing disease of the brain and spinal cord where aquaporin-4 (AQP4) water channels are the main antigenic target (1). The disease involves regions of the central nervous system (CNS) where water channels are widely expressed. The diagnostic criteria for NMOSD incorporate six clinical presentations involving different areas of the CNS including the spinal cord causing longitudinally extensive transverse myelitis (LETM), the optic nerve causing optic neuritis (ON), the medulla causing area postrema syndrome, the brainstem causing acute brainstem syndromes, and the thalamus/hypothalamus causing acute diencephalic syndromes (1, 2). The occurrence of one of the above-mentioned syndromes in the presence of serum AQP4-IgG + autoantibodies makes the diagnosis of AQP4-IgG+ NMOSD (2).

As NMOSD attacks can lead to significant long-term disability, pharmacotherapy aims at aggressively treating acute inflammatory attacks and prevent future attacks to reduce CNS damage and preserve neurologic function (3, 4).

The management of NMOSD includes acute as well as long term treatment (3). Acute attack is typically treated with high dose intravenous corticosteroids in the form of 1 gram of methylprednisolone daily for 5 days followed by gradually tapered doses of oral prednisone, typically over months in selected cases. If improvement is not seen within days of corticosteroids, plasma exchange (PLEX) or immunoadsorption are possible options (3–5) Some experts in the field suggest the use of PLEX or immunoadsorption as a first line treatment option in the treatment for subsequent attacks, especially for LETM (4, 5).

NMOSD is a devastating disease where if patients are left untreated will suffer Long term complications (1, 2) Many medications have been used for long term immunosuppression such as Rituximab, Mycophenolate, and Azathioprine with variable success rates (3). Most recently, three monoclonal antibodies (Table 1) have been approved by the United States Food and Drug Administration (FDA) for the treatment of NMOSD. The year 2019 is thought to be the "year of the NMO" when 3 new drugs became available as treatment options for this otherwise devastating disease (3). In this paper, FDA approved medications for adult onset NMOSD will be reviewed in detail.

Eculizumab

Eculizumab is a humanized monoclonal antibody that has been tried in NMOSD with favorable results. Eculizumab is a terminal complement inhibitor that prevents the C5 convertases from associating with C5, which in turn prevents C5 cleavage to the proinflammatory complement component C5a and C5b (6). It has been used in paroxysmal nocturnal hemoglobinuria, atypical Hemolytic uremic syndrome as well in refractory seropositive generalized Myasthenia Gravis. AQP4 IgG has shown in cell-based assays to induce a potent complement mediated toxicity, which could likely explain the utility of a complement inhibitor in treatment of NMOSD. The recommended dose of Eculizumab is 900 mg every week for initial four doses, followed by 1200 mg every 2 weeks (6). Early studies of this drug by Pittock et al. on 14 patients showed reduced relapse in AQP4-IgG+ NMOSD (6). Pharmacokinetics data have shown that Eculizumab achieves steady state concentration by about week 4 and thereon, complement inhibition is noted by Day 1 of infusion through the pre-dosing trough levels, thus suggesting early and sustained action of the drug (7). The PREVENT trial was a multicenter, randomized, double-blind, time-to-event trial from 18 countries where 143 adults were randomized to receive either intravenous eculizumab or placebo. The study included AQP4 IgG positive patients who had 2 attacks in previous 6 months (8) The annualized relapse rate in the past 24 months prior to initiation of Eculizumab was comparable between both groups (1.94 vs 2.07) (8). Transverse myelitis was the most common followed by optic neuritis then brainstem and cerebral symptoms (6). On comparison of the annualized adjudicated attack rate between the 2 groups at the end of the study the Eculizumab group was 0.02 in contrast to the placebo group of 0.35. The first adjudicated attack was seen in 3% of the Eculizumab group and 20% of the placebo group. Per study results "The proportions of eculizumab- and placebo-treated patients who remained attack-free were 97.9% and 63.2% respectively at week 48, 96.4% and 51.9% respectively at week 96, and 96.4% and 45.4% respectively at week 144" (7, 8). The attack free rate was lower (more attacks noted) in the subgroup of the placebo cohort that was not on any other immunosuppressive agent (6). A subgroup analysis on the Asian population included in the study suggested Eculizumab was equally effective with a similar side effect profile in this subgroup and this similar efficacy was noted in the *post hoc* subgroup analysis across different age group, races, sex as well as geographic location (9).

Upper respiratory tract infection, headache, nausea, nasopharyngitis were some of the reported side effects from the study. The most important precaution is initiating meningococcal vaccination (against serogroups ACWY and B) prior to starting on Eculizumab. It is recommended that patients receive the required booster vaccination for meningococcal meningitis for the duration that they are on Eculizumab as there is significant 1000-fold increase in risk of meningococcal disease in comparison to the general U.S. population due to complement factor inhibition which are essential components against fighting the meningococcal bacteria (6). Though the advisory committee on Immunization

TABLE 1 FDA approved medications for NMOSD.

Medication	Mechanism of Action	Clinical Trial/s	Recommended dosage	Reported side effects
Eculizumab	C5 monoclonal antibody	PREVENT trial	900 mg every week for initial four doses, followed by 1200 mg every 2 weeks	Meningococcal infection, upper respiratory tract infection, headache, nausea, nasopharyngitis.
Satralizumab	Blocks IL-6 signaling pathway	Sakurastar and Sakurasky trial	Initial injection of 120 mg, followed by another injection at week 2 and week 4 as loading doses, followed by a maintenance dose of 120 mg every 4 weeks	headache, arthralgia and injection site reactions.
Inebilizumab	Anti-CD19 monoclonal antibody	Phase II-III N-Momentum trial	Intravenous infusion with 2 initial doses of 300mg separated by 2 weeks and followed by 300mg every 6 months	infection and infusion related reactions

practice recommendation in Eculizumab is for meningococcal vaccination only, there is theoretical risk for increased infection from encapsulated organisms, hence clinicians need to consider vaccination for H. Influenza and Pneumococcal infections. It is recommended to receive antibiotic prophylactic coverage if the infusion was initiated in less than 14 days of having received the vaccination (6, 8). Between 2006-2018, there were a total of 16 reported cases of meningococcal disease in patients receiving Eculizumab, 14/16 who had received the vaccination. It was however noted that 11/16 were non-groupable (10).

However, the study involved only AQP4-IgG seropositive patients and we are unable to extrapolate the same results for seronegative patients. The study extended into an open label study after completion of the short 6 week follow up when the trial was terminated early. On the open label extension, per the paper "At 192 weeks (4 years), 96% patients were adjudicated attack free. 95% (20/21) of patients on Eculizumab were stable and had no disability worsening thus providing effective long-term relapse prevention, making it a desirable drug in patients requiring long term therapy for this disabling disease" (6, 11). Relative to placebo, per the paper "Eculizumab showed significant reduction in the annualized rate of adjudicated attack-related hospitalization (0.012 vs. 0.267; $p < 0.0001$), use of IV methylprednisolone (0.012 vs. 0.286; $p < 0.0001$), high-dose oral corticosteroids (0.012 vs. 0.114; $p = 0.0021$) and PLEX (0.012 vs. 0.134; $p = 0.0006$)" (6, 11).

Some questions that remain are the effect from concomitant use of immunosuppressive agents in almost 70% of patients, efficacy of the agent in seronegative patients, and safety profile in pregnant women as currently there is no available data on the same.

Ravalizumab is a C5 complement inhibitor with a similar mechanism as Eculizumab, the efficacy and safety of which was reported in a phase III clinical trial, the CHAMPION-NMOSD. The study revealed that Ravalizumab significantly reduced the relapse rate while maintaining a good safety profile. The main advantage over Eculizumab was longer dosing interval as compared to Eculizumab due to longer half-life (12).

Satralizumab

Satralizumab is a humanized immunoglobulin G2 monoclonal antibody that has been developed for the treatment of NMOSD and was approved for first time use in Canada in June of 2020 as monotherapy or as combination therapy in adults and children 12 years or older who are positive for AQP4-IgG autoantibodies (13, 14). Satralizumab was subsequently approved by the US FDA for the same indication on 17 August 2020 (15).

The medication is given subcutaneously and comes in a 120 mg/ml prefilled syringe designed for single use. The currently used dose includes the initial injection of 120 mg, followed by another injection at week 2 and week 4 as loading doses, followed by a maintenance dose of 120 mg every 4 weeks (14). Following the administration of the medication at the recommended dose, the half-life is close to three days and the bioavailability is 78.5% (15).

Although the mechanism of action of Satralizumab is not well understood, it is thought to be mediated through blocking of Interlukin-6 (IL-6) signaling pathways which results in reduction of inflammation and IL-6 mediated autoimmune T- and B-cell activation (16). Satralizumab binds to membrane-bound and soluble IL-6 receptors. This binding results in preventing IL-6 from binding to its substrate and subsequently inhibiting the IL-6 signaling pathways involved in inflammation. The inhibition of T and B cells eventually prevents the differentiation of B cells into AQP4-IgG-secreting plasma cells (16, 17). Due to a unique recycling technology, Satralizumab detaches from IL-6 receptor in a pH-dependent medium which in turn prolongs the duration of circulation in the body (16, 17).

SAkuraStar and SAkuraSky are 2 multinationals, randomized, double-blind, placebo-controlled phase III trials that evaluated the safety and efficacy of Satralizumab in patients with NMOSD (both AQP4-IgG seropositive and seronegative). Briefly, in the SAkuraStar trial patients were randomized 2:1 to receive Satralizumab monotherapy or placebo, while in the SAkuraSky trial, patients were randomized 1:1 to receive Satralizumab add on (in combination with their baseline immunotherapy) or placebo (16). Baseline immunotherapy included azathioprine, mycophenolate mofetil, or oral corticosteroids. For children aged 12 to 17 years at time of enrollment, baseline treatment with azathioprine or mycophenolate mofetil in combination with oral corticosteroid was also permitted (14, 15). Alone or in combination with baseline immunotherapy, Satralizumab was effective in reducing the risk of a judicially considered NMOSD attack (16).

In the SAkuraStar trial, the number of patients who experienced an attack was significantly lower (p = 0.018) in the Satralizumab monotherapy group compared to the placebo group (30% vs 50%). The trial found an attack reduction risk of 55% (16). In the SAkuraSky, a significantly lower number of patients in the add-on Satralizumab group experienced an attack compared with the placebo group (20% vs 43%), with Satralizumab reducing the risk of relapse by 62% (16). While attack rate reduction was shown to be significant in patients who are AQP4-IgG positive, there was insufficient evidence that Satralizumab lowered the risk of NMOSD relapse in patients who were seronegative for AQP4-IgG autoantibodies (17).

Satralizumab was shown to be well tolerated in patients with NMOSD. The trials reported the following adverse effects; headache, arthralgia and injection site reactions (17). In about 2.9% of patients who received the medication, serious adverse events including infection were reported. No anaphylactic reactions or deaths were reported in either of the clinical trials (17).

It is worth mentioning that Tocilizumab which has an off label use might be a safe and effective medication to prevent attacks in patients with NMOSD. In the TANGO trial, Tocilizumab was found to significantly reduce the risk of NMOSD attacks when compared with azathioprine (18) but has a lower level of evidence since the trial was only an open label, multicentre, randomized phase 2 trial.

Inebilizumab

Inebilizumab is a humanized afucosylated monoclonal antibody that targets CD-19 expressing B cells (19–21). It has been approved

by the US FDA in 2020 for the treatment of anti-AQP4 antibody positive NMOSD. It has also been used in several other countries (19–21). It is given as intravenous infusion with 2 initial doses of 300mg separated by 2 weeks and followed by 300 mg every 6 months (21).

B cells have a major role in the pathogenesis of NMOSD. Inebilizumab is a B cell depleting drug that has high affinity to CD-19 expressing B cells and initiates antibody mediated cellular cytotoxicity and cellular phagocytosis. FcRIIIA is a receptor that mediates antibody-dependent cytotoxicity and afucosylation of Inebilizumab increases the affinity by nine-fold to the binding site (19, 21) B cell depleting agents have been studied in the past for management of NMOSD relapses (19–21). Rituximab is one of the medications that has been used off label for treatment of NMOSD. It acts by depleting the CD 20 expressing B cells whereas Inebilizumab acts on CD-19 expressing B cells. CD-19 is also expressed on the pro-B stage of B cells and widely expressed than CD-20. AQP4-IgG antibodies have been produced at various stages of the B cell life cycle and many research studies have focused on CD-19 positive B cells in the management of antibody positive NMOSD (19, 21).

The safety and efficacy of Inebilizumab were evaluated by an international, multicenter, randomized, double-blind, placebo-controlled Phase II/III trial called N-MOmentum study with open-label extension period (19–21). The study included both AQP4-IgG seropositive and seronegative patients. The percentage of seronegative patients was too low for meaningful subgroup analysis. The duration of the randomized control time was about 28 weeks. It was found that at 28 weeks, this medication was effective in reducing the attack rates of NMOSD as monotherapy. During the 28 weeks of treatment, patients treated with Inebilizumab had reduced worsening of the disability with associated fewer lesions on MRI and reduced hospital stay (19–21). Studies have shown that there was a significant reduction of B cells during the treatment. The long-term safety was assessed by the open-label extension period which showed that the effect lasted for more than 4 years (20, 21). Complications like infusion related reactions, arthralgias and infection were similar between the placebo group and Inebilizumab group (19, 20, 22).. Reduced efficacy to vaccination was noted as a consequence of b cell depletion. Inebilizumab also led to a decrease of serum GFAP, as a disease activity biomarker. According to N-MOmentum study, GFAP levels decreased by 12.9% in participants treated with Inebilizumab (21, 23).

Ongoing clinical trials

Many clinical trials are currently investigating other medications for the efficacy and safety in NMOSD. Some of these medications include the following;

Belimumab

Belimumab is a monoclonal antibody that has been previously approved for the treatment for use in Systemic Lupus Erythematosus (SLE). The antibody works *via* neutralizing B cell stimulator. A phase II clinical trial is looking at time to relapse in patients with NMOSD while being on monthly Belimumab injections after initial loading. The results are expected in January 2023 (24).

Bevacizumab

Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor A. It is currently being evaluated in a drug trial for the treatment in NMOSD. In this trial, a single infusion of bevacizumab is administered in addition to high dose corticosteroids and an additional dose of Bevacizumab is added to PLEX if indicated. The preliminary results have showed promising results that need to be further investigated (25).

HBM9161(HL161BKN)

HBM9161(HL161BKN) is a human monoclonal antibody which is currently under an open label dose exploration phase 1 trial. HBM9161 acts by blocking neonatal Fc receptor (FcRn) which is an IgG-Fc binding site and accelerates the breakage of IgG and since AQP4-IgG associated with NMOSD is a pathological IgG, it is supposed to be beneficial by rapidly reducing AQP4-IgG levels (26). Of note, FcRn blockade has been proven to be effective in myasthenia gravis (27).

Conclusion

The recent advancement in our understanding of the pathophysiology of NMOSD has revolutionized the management options and resulted in the introduction of new and safe medications. The newer medications have the ability to target specific elements of the autoimmune cascade in patients with NMOSD. Head-to-head comparisons of (on- and off-label) biological agents for treatment of NMOSD are not available and the differential indication is a matter of ongoing debate. Despite the great success in seropositive patients, the insufficient response in seronegative patients calls for further investigation and more clinical trials.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Optic disc drusen and scleral canal size – protocol for a systematic review and meta-analysis

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Background: Around one in forty patients are diagnosed with optic disc drusen (ODD) during their lifetime. Complications of these acellular deposits range from asymptomatic visual field deficits to artery occlusion and subsequent cecity. Still, the pathogenesis of their emergence remains controversial. In particular, it was suggested 50 years ago that a narrow disc and scleral canal is one factor leading to axoplasmic flow disturbance, which induces ODD formation. However, this hypothesis is still debated today. To evaluate the basis of this theory, we will conduct a systematic review and meta-analysis of studies evaluating the scleral canal size in patients with ODD and in healthy subjects.

Methods: We will search MEDLINE via PubMed, Cochrane, and EMBASE electronic databases to identify articles published before November 29, 2022 that measure the scleral canal size in patients with ODD and in healthy subjects. In addition, grey literature will be searched. The meta-analysis will include studies that include patients with a clinical or imaging diagnosis of ODD and healthy subjects. Additionally, we will perform a subgroup analysis to compare patients with buried ODD and patients with visible ODD. Extracted data from included studies will be presented descriptively, and effect sizes will be computed based on the recommendations from the Cochrane Collaboration handbook.

Discussion: The hypothesis that a narrow scleral canal is a risk factor of ODD has long been debated and this systematic review and meta-analysis should disentangle the different views. Understanding the underlying factors driving the development of ODD should help us focus on patients at risk and develop strategies to prevent advanced stages of the disease in these patients. Besides, focusing on patients with small scleral canals should help us derive associated factors and provide a better understanding of the pathology.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022375110.

KEYWORDS

optic nerve head drusen, optic disc drusen, scleral canal, Bruch's membrane opening, disc size, crowded disc

1 Introduction

Optic disc drusen (ODD) are acellular deposits that are thought to result from axonal disintegration following axoplasmic flow disruption in the optic nerve head (1). The reported prevalence in adults varies from 0.2% (2) to around 2.0% (3, 4). Only 0.4% of children are thought to be affected. The diagnosis is often made incidentally in children with pseudo-papilloedema (5, 6) or in adults with visible drusen overlying the border of the disc. However, more than half of the patients have visual fields deficits (blind spot enlargement, field constriction) due to retinal nerve fiber layer atrophy (7) and a small number of patients with large ODD will develop dramatic complications, such as choroidal neovascularization, central artery occlusion or anterior ischemic neuropathy (8–12). Understanding underlying risk factors could allow clinicians to screen patients at risk and undertake a more specific follow-up to evaluate the evolution of the ODD and their consequences.

It has long been proposed that ODD are more likely to emerge in patients with a narrow scleral canal, as the latter is the location of increased axonal mechanical constraints. Several studies have been undertaken to test this hypothesis, but with diverging results (13–15). However, several factors – including the location of the ODD, the age of the patients, the instrument for measurement – are likely to influence the outcome. Therefore, the association between the presence of ODD and the size of the disc and scleral canal would be worth exploring in a systematic way.

The anterior opening of the optic nerve scleral canal is, by definition, the anatomic entrance to the scleral canal at the level of the sclera. It is mostly evaluated using either fundus pictures, where it corresponds to the limits of the disc, or optical coherence tomography (OCT). In most studies, measurements at the level of the Bruch's membrane opening (BMO) are considered as proxies of the measurements at the level of the anterior opening of the optic nerve scleral canal (16, 17). Indeed, the BMO is well defined on OCT (14, 15, 18, 19) and seems to remain stable over time and conditions (17, 20). The high-resolution enhanced depth imaging spectral-domain OCT (EDI SD-OCT) and swept source OCT (SS-OCT), in particular, provide a greater penetration and a better characterization of deep structures, with less artefacts induced by the drusen themselves (21). EDI-SD-OCT with scan averaging is the ODD diagnostic modality recommended by the Optic Disc Drusen Studies Consortium (22). It has proven equivalent to SS-OCT in that regard (21).

This systematic review and meta-analysis will thus aim at evaluating the mean difference of the scleral canal size at the level of the BMO between patients with ODD and healthy controls, with a secondary focus on patients with buried ODD versus patients with visible ODD.

Two main objectives will be evaluated:

- Mean difference of the scleral canal size at the level of the BMO using fundus pictures between patients with ODD and healthy controls.
- Mean difference of the scleral canal size at the level of the BMO using OCT (SD-EDI or SS) between patients with ODD and healthy controls.

Because we expect that patients with buried ODD and patients with visible ODD might differ, we will also undergo a subgroup analysis and compute the following outcomes:

- Mean difference of the scleral canal size at the level of the BMO using fundus pictures between patients with buried ODD and patients with visible ODD.
- Mean difference of the scleral canal size at the level of the BMO using OCT (SD-EDI or SS) between patients with buried ODD and patients with visible ODD.

Abbreviations: EDI, enhanced depth imaging; HS, Healthy subject; OCT, optical coherence tomography; ODD, Optic disc drusen; SD-OCT, spectral domain optical coherence tomography; SS-OCT, swept source optical coherence tomography; TD-OCT, time-domain optical coherence tomography.

2 Methods/design

The literature search and analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (23) (see Supplementary File 1) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) (24) guidelines.

2.1 Search strategy

We will search MEDLINE via PubMed, Cochrane, and EMBASE electronic databases to identify articles published before November 29, 2022 that measure the mean difference of the scleral canal size at the level of the BMO between patients with ODD and healthy controls or between patients with buried ODD and patients with visible ODD. In addition, grey literature will be searched in Google Scholar, Greylit.org, World Health Organization Clinical Trials Search Portal, ClinicalTrials.gov and the European Union Clinical Trials Register. All reference lists and bibliographies of included studies will be reviewed for potentially relevant studies that could be missed by this literature search.

The search will involve the following MeSH keywords: optic AND (disk OR disc OR nerve) AND drusen AND (canal OR area OR size OR measure OR crowded OR small).

2.2 Inclusion criteria

Randomized controlled and non-randomized controlled trials, as well as observational studies will be eligible for inclusion. Inclusion criteria will be patients with a clinical or imaging (autofluorescence, B-scan ultrasound, OCT, CT scan) diagnosis of ODD.

2.3 Exclusion criteria

Articles with previously published data (review, meta-analysis, follow-up study) and case reports will be excluded. We will exclude

articles of studies that do not include people with ODD, that do not quantify the size of the scleral canal, that do not have a control group (either HS for patients with ODD or visible ODD for patients with buried ODD) or that include only syndromic ODD (ODD associated to a known predisposing syndrome, such as Pseudoxanthoma Elasticum, Retinitis Pigmentosa, Usher syndrome, Down Syndrome, Alagille Syndrome, Noonan syndrome).

We will exclude from the meta-analysis (but include in the systematic review and the sensitivity analysis) studies relying on time-domain OCT (TD-OCT) or non-EDI SD OCT for performing the measurements of the scleral canal size at the level of the BMO. Likewise, for the second main objective and subgroup analysis (measurements based on OCT), only the studies relying on gold standards state-of-the-art OCT (EDI SD OCT or SS OCT) to exclude ODD and define normal optic nerve according to the Copenhagen Consortium (15) will be included. Articles that do not provide appropriate data for pooling the outcomes despite authors being contacted for missing material will also be excluded. Data (reported or obtained from one of the authors) will be considered sufficient in one of the three following situations: sample sizes, means and standard deviations for both groups considered; sample sizes, medians and all four quartiles for both groups considered; raw values for every patient for both groups considered.

2.4 Review process

Figure 1 is a PRISMA flow chart of the review process. Potentially eligible studies will be screened for eligibility by AVJ. We will import articles to Zotero, and all articles will be reviewed (title, abstract and main text when needed) to discard those that do not meet the criteria. Data of included papers will then be extracted and the studies will be assessed for risk of bias.

2.5 Risk of bias appraisal

We will assess the quality of included studies through a domain-based quality assessment grid adapted from the National Institutes of Health quality assessment tool of case-control studies (25, 26). The assessment will be performed independently by two review authors (AVJ and MR), each blinded to the score given by the other. They will later discuss discrepancies until they reach consensus. If no consensus is reached, a third author (DBG) will arbitrate. Publication risk of bias will be characterized using Egger's statistical test and visual inspection of the funnel plot, which represents the estimated effect size (horizontal axis) versus its standard error mean (vertical axis). Asymmetry of the inverted funnel shape favors publication bias.

2.6 Data extraction and analysis

2.6.1 Study review

Upon selecting articles for inclusion, all references will be imported in Microsoft® Excel (version 16.65) for data extraction. One assessor (AVJ) will extract and collate information. Another assessor (MR) will verify the extracted material from all included articles. The following data will be extracted (see Supplementary File 2):

- Study characteristics: authors, title, year of publication, inclusion and exclusion criteria, sample size;
- Population characteristics: percentage of buried versus visible drusen, age, spheric equivalent
- Outcome measure characteristics: type of the parameter, means and standard deviations (or median and interquartile range (IQR)), OCT type if appropriate, magnification correction formula if applied

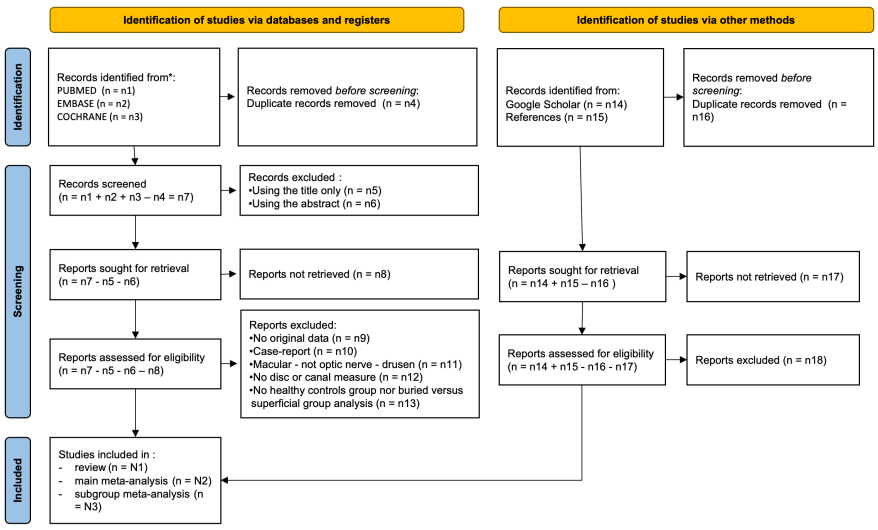

FIGURE 1
PRISMA flow chart of the review process.

- Statistical analysis: test for normality, test used, whether correction for multiple comparison was applied, confounding factors, parameter significance.

The data extraction tables will be pilot-tested and refined before extraction.

The means and standard deviations will be extracted when available. If the results are reported using medians and IQR, we will search the protocol – if available – and methods to determine whether the data was shewed or whether it was a preference of the authors and there had been no test of normality although the sample size was large enough to expect a Gaussian distribution. In case the choice is not explained and the sample size is above 50, we will suppose a normal distribution and apply the following transformation formulæ: *mean* = *median* and $SD = \frac{IQR}{1.35}$. In any other case, we will use the formulæ by Luo et al. (27) and Shi et al. (28):

$$mean = w_1\left(\frac{a+b}{2}\right) + w_2\left(\frac{q_1+q_3}{2}\right) + (1 - w_1 - w_2)\,.\,median$$

where $w_1 = \frac{2.2}{2.2+n^{0.75}}$ and $w_2 = 0.7 - \frac{0.72}{n^{0.55}}$.

$$\text{and } SD = \frac{b-a}{\theta_1(n)} + \frac{q_3 - q_1}{\theta_2(n)}$$

where $\theta_1(n) = (2 + 0.14n^{0.6})\,.\,\phi^{-1}\left(\frac{n-0.375}{n+0.25}\right)$, $\theta_2(n) = \left(2 + \frac{2}{0.07n^{0.6}}\right)\,.\,\phi^{-1}\left(\frac{0.75n-0.125}{n+0.25}\right)$ and $\phi^{-1}(z)$ is the upper z^{th} percentile of the standard normal distribution, and a is the minimum value, q_1 the first quartile, q_3 the third quartile and b the maximum value.

If neither one of those data is available, the raw data will be sought and retrieved. If none of this material is available, it will be requested from the corresponding author (he will be contacted up to three times via e-mail). If this latter cannot provide the information, the study will be excluded from the meta-analysis.

When data are not available in the main text, we will search Supplemental Materials for more detailed information. If data are only available by graphical representation, the assessors (AVJ and MR) will use Plot Digitizer to extract data from graphs: the final value will be the mean of these two extractions.

2.6.2 Strategy for data synthesis

Extracted data from included articles will be presented descriptively, and effect sizes will be computed based on the recommendations from the Cochrane Collaboration handbook. and Cochrane Review Manager v5.3.

Our preliminary search suggests that the mean diameter and the total area of the optic disc are two common parameters used to describe the optic disc size. Because the calculation of the mean diameter is more straightforward, we will report the mean diameter only. In cases where the mean diameter is not reported, we will transform the reported measure using the following formulas, which suppose that the optic disc can be approximated by a disc (29):

- The reported measure is the maximal and minimal diameters: mean diameter $= \frac{\text{maximal diameter + minimal diameter}}{2}$
- The reported measure is the horizontal diameter: mean diameter = horizontal diameter
- The reported measure is the total area: mean diameter $= 2 \times \sqrt{\frac{total\ area}{\pi}}$.

Extracted data will then be pooled to derive Hedge's standardized mean difference. We will apply a fixed-effects model when the I^2, the percentage of variation across studies due to heterogeneity rather than chance, was low to moderate ($I^2 < 50\%$) (30, 31); otherwise, we will perform a random-effects model. The 95% confidence interval excluding the null value will be considered significant. The between-study variance, τ^2, will be estimated using the Restricted Maximum-Likelihood formula (30).

We will use R v4.0.3 with the 'Metafor' package for the statistical analysis and the plots.

2.6.3 Sensitivity analysis

Two sensitivity analysis will be performed.

First, we will explore the impact of the hypothesis that the disc can be approximated by a disc. To that end, we will analyse only studies that computed the mean diameter.

Second, we will explore the impact of choosing only studies with recent state-of-the-art OCT modalities. To do so, we will add studies using TD-OCT and non-EDI SD OCT to the analysis.

In both cases, reporting will be done in a summary table.

The overall quality of the evidence for each outcome will be evaluated by using the GRADE criteria following the Cochrane Collaboration recommendations if enough RCTs and interventional studies are included (32).

3 Discussion

Identifying the factors responsible for the emergence of ODD may help develop a better screening protocol and prevent dramatic complications through earlier diagnosis and care. We are not aware of any means to enlarge the scleral canal: therefore, it would not be a modifiable risk factor. Neither are we able to predict the impact of widening the scleral canal. However, should this study support the association between a narrow scleral canal and the presence of ODD, it would allow defining a better population for studies evaluating the impact of modifying other potential risk factors or introducing preventive treatments. In that regard, the potential interest of lowering the intra-ocular pressure is still pondered (33) and neuroprotective treatments are being developed, which might also prove useful to halt the progressive atrophy in patients with ODD (34–36).

Several observations support the hypothesis that a narrow scleral canal plays a central role in the formation of ODD. Genetic factors have been incriminated, which follow an irregular autosomal dominant pattern, and small optic discs have been observed in affected families (1). ODD are mainly found in caucasians, who have a smaller optic disc compared to African and Asian people (37, 38). ODD are more frequent in rod-cone dystrophies, and in particular in Usher syndrome, where scleral canals have been found smaller than in other dystrophies (39). In healthy subjects, the optic disc size correlates to the axial length (40). It is therefore interesting to note that the prevalence of ODD in nanophtalmos and posterior microphthalmos is higher than in the

general population (41–43). In nanophtalmos, the presence of ODD correlates to the axial length (41). Pseudoxanthoma elasticum is another disease associated to the presence of ODD (44). If, to our knowledge, no direct link has been unveiled with the scleral canal size, it is remarkable that this pathology is characterized by ectopic mineralization in elastic fibers, and in particular in the Bruch's membrane, which then becomes rigid. We can suppose that its opening turns out to be a zone of higher constraint for the nerve fibers.

Other hypotheses have been put forward: in particular, it has been proposed that ODD emerge from abnormal vasculature and branching, as higher frequencies of trifurcation and cilioretinal arteries have been observed in patients with ODD (45, 46). An abnormal permeability and a deficient blood barrier would induce chronic ischemia and calcium deposition, leading to ODD formation. Still, an association has been found between a small scleral canal and vascular anomalies in ODD patients (47), and it is possible that abnormal vessels are a consequence of the higher constraints induced pre- and post-natally by a narrow canal.

We acknowledge several limitations to this study. Although we will adhere to the PRISMA guidelines and methodology, it is not possible to completely account for the limitations of included studies. We expect moderate to high heterogeneity because of several variable factors, including patients' age, measurement methods or magnification correction. However, these factors will be discussed in the narrative review, which will allow us to examine the results accordingly. A subgroup analysis taking into account the expected difference between buried ODD and visible ODD might help us explain part of the heterogeneity and the divergency observed in the literature. To limit the file drawer problem which results in publication bias, grey literature will be searched in addition to traditional databases of published literature.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

AV-J: Conceptualization, Writing – original draft, Writing – review & editing. DB-G: Conceptualization, Writing – review & editing. MR: Conceptualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Giant cell temporal arteritis: a clinicopathological study with emphasis on unnecessary biopsy

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Introduction: Temporal artery (TA) biopsy is commonly used for the diagnosis of giant cell arteritis (GCA). However, a positive biopsy is no longer mandatory for diagnosis. This study aims to correlate the histopathological findings of TA biopsies in suspected cases of GCA to the clinical presentation in an ophthalmic tertiary eye care center to draw useful conclusions and advocate the possible implementation of guidelines for TA biopsy.

Methods: Data was collected from patients' medical records including, demographics, clinical data, and histopathological findings and diagnosis. The 2022 American College of Rheumatology/ European Alliance of Associations for Rheumatology (ACR/EULAR) criteria have been used and partially adopted as a guide to compare the variables between TA biopsy-positive and negative groups as well as the TA biopsy-positive group and the group of patients with TA biopsy showing atherosclerosis.

Results: Out of the total 35 patients who underwent a TA biopsy during the period of 23 years, 22.9% of patients had histopathological findings consistent with GCA and 42.9% had TA atherosclerotic changes, while the remaining 34.3% had histologically unremarkable TA. The mean age of all patients was 66 $\pm$ 10.9 years. Slightly more than half were females (54.3%) and the remaining were males (45.7%). In the group with positive TA biopsies, the mean age was 71 $\pm$ 8.4 years with a higher female predominance (female-to-male ratio of 5:3). The mean diagnostic clinical score used in our study was higher (7.5 $\pm$ 2.33) in the GCA-positive group when compared to the other groups with statistical significance (mean of 4.85 $\pm$ 2.01 in patients with overall GCA-negative biopsies and 5.13 $\pm$ 2.10 in the group with atherosclerosis). Other three clinical variables that were found to be statistically significant in the GCA biopsy-positive group were scalp tenderness, jaw claudication, and optic nerve pallor.

Discussion: The mean age (71 $\pm$ 8.4 years) and the female predominance of GCA in our group of patients with positive TA biopsy (62.5%) was like other reports. In our study 22.9% of performed TA biopsies over the period of the study were positive confirming the diagnosis of GCA on histological exam, which was similar to another report and is considered to be relatively low. The incorporation of increased clinically focused assessments and algorithms, with the aid of the ACR/EULAR criteria, may decrease the frequency of TA biopsies that carries

unnecessary cost and risk of procedure-related morbidity. We highly recommend applying the age of ≥ 50 years as an initial criterion for diagnosis, followed by the consideration of the statistically significant clinical features: scalp tenderness, jaw claudication, and optic nerve pallor.

KEYWORDS

giant cell arteritis, temporal artery, ischemic optic neuropathy, temporal artery biopsy, atherosclerosis, optic nerve

1 Introduction

Giant Cell Arteritis (GCA) is a large-cell vasculitis that preferentially affects large to medium-sized arteries. GCA most commonly develops in those over the age of 50 with a peak incidence in the eighth decade of life and a slight female predominance (Female to male ratio of 3:1). Globally, GCA incidence varies. The highest recorded incidence is found in Northern Europe (44/100,000 persons over 50) and the lowest in Sothern Asia (0.3/100,000). In the Middle East, the incidence ranges from 4.9 to 11.3 per 100,000 persons over 50 (1). It has a particular affinity for the branches of the external and internal carotid arteries, including the temporal artery, hence the term temporal arteritis (2). Genome-wide association studies have found that polymorphisms in the HLA-DR region are highly linked to the GCA autoimmune response (3). This response includes interactions between the innate and adaptive immune system, that trigger granulomatous inflammation in the tunica media and destruction of the arterial wall's elastic tissue. As a result, temporal artery (TA) biopsies have long been the gold standard for diagnosing GCA. However, according to the American College of Rheumatology (ACR), a positive TA biopsy is not mandatory for the diagnosis of GCA (4). The 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) have also developed classification criteria as a guide for diagnosing GCA (5). Therefore, in a setting of a tertiary eye center with limited or no access to a highly specialized rheumatology unit (to aid in the clinical diagnosis), unnecessary TA biopsies may be performed. The aim of this study is to correlate the histopathological findings of TA biopsies in our eye center to the clinical presentation. This will emphasize the importance of developing proper clinical and diagnostic criteria and highlight possible guidelines for TA biopsy performance in suspected cases.

2 Materials & methods

This is a retrospective study of all TA biopsies that were received by the Pathology and Laboratory Medicine Department, King Khaled Eye Specialist Hospital (KKESH) during the period: June 2000 to June 2023. The corresponding patients' medical records were reviewed to collect demographics, and clinical information including the clinical symptoms, signs, duration of presentation, and relevant laboratory investigations as well as biopsy information (date and results), using a special data collection sheet. The initial histopathological data included a total of 38 unilateral TA biopsies received over the above study period. Demographic and clinical data were not available in three patients thus, they were excluded. 35 cases have been included for analysis in this study.

The 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria have been used as a guide to compare the TA biopsy-positive group and TA biopsy-negative group (Supplementary Material). We have adopted a GCA diagnostic score assigned to each patient that excludes laboratory investigations and the scoring for the TA biopsy itself. The diagnostic scoring system includes the following: morning stiffness in the shoulders/neck, sudden visual loss, jaw or tongue claudication, new temporal headache, scalp tenderness, and abnormal examination of the temporal artery. For each positive sign or symptom, two points were given, except for sudden visual loss, for which three points were given. The available erythrocyte sedimentation rate (ESR) was used as a separate variable, independent of the modified scoring mentioned above. C-reactive protein (CRP) measurement was not done for most patients and thus, was not included as a variable in our analysis.

The variables used in our baseline analysis to calculate the aforementioned diagnostic score are highlighted in Table 1. According to the ACR/EULAR guidelines, which include laboratory investigations, imaging (ultrasound and PET) results, and biopsy results, any score greater than or equal to six, is needed for the classification of giant cell arteritis (5). Since we did not have availability for all tests included in the guidelines, and considering our goal of comparing the diagnostic clinical criteria between the two patient groups to justify performing a TA biopsy, we did not enforce the cut-off scoring of six on our cases. Rather, we have utilized the clinical items in the ACR/EULAR guidelines as variables, to indicate by analysis, the potentially important items that showcase a statistically significant difference between the two groups. As a result, these variables can aid in the pre-biopsy clinical judgment and diagnosis of GCA, and can guide ophthalmologists in their decision to proceed further with a TA biopsy or not. Other significant signs and symptoms that were recorded apart from the ones used in the ACR/EULAR guidelines, were noted as well in the same table.

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TABLE 1 Comparison between the GCA biopsy-positive and biopsy-negative groups.

Variables		Biopsy Results				*p* (<0.05)
		GCA Positive (n = 8)		GCA Negative (n= 27)		
		Frequency	%	Frequency	%	
Components of Diagnostic Score	Sudden visual loss	8	100	23	85.2	0.553
	New temporal headache	5	62.5	19	70.4	0.685
	Jaw or tongue claudication	3	37.5	2	7.4	0.067*
	Morning stiffness in shoulders and/or neck	1	12.5	3	11.1	>0.999
	Scalp tenderness	7	87.5	5	18.5	**0.001**
	Abnormal temporal exam	2	25.0	4	14.8	0.602
Corresponding Diagnostic Score (mean ± SD)**		7.5 ± 2.33		4.85 ± 2.01		**0.003**
Neck pain		2	25.0	3	11.1	0.568
Sweats		0	0.0	4	14.8	0.553
Generalized weakness		2	25.0	3	11.1	0.568
Optic nerve changes		6	75.0	21	77.8	>0.999
Optic nerve pallor		6	75.0	8	29.6	**0.039**
Elevated ESR (≥50 mm/hr)		7	87.5	22	81.5	>0.999

GCA, Giant cell arteritis * This p-value was re-assessed by comparing the eight GCA-positive patients to the 12 patients with normal TA biopsy findings & was found to be statistically significant with p = 0.049. **Defined as all of the items mentioned above the score (i.e., sudden visual loss, new temporal headache, jaw or tongue claudication, morning stiffness in shoulders and/or neck, scalp tenderness, abnormal temporal artery exam).
Bold values are statistically significant P values.

Data was analyzed using "SPSS" Version 20.0. Categorical variables are presented as percentages and frequencies and are compared using the Fisher's Exact Test. Clinical scores are presented as a mean ± standard deviation and were compared using the Independent Samples T-test. The *p* values mentioned are all two-sided, and *p* values <0.05 were considered to denote statistical significance. This study was prepared in accordance with the ethical standards of the human ethics committee (HEC) at KKESH and expedited approval as a retrospective study from the HEC/IRB of the Research department in accordance with the Helsinki Declaration.

3 Results

Thirty-five patients who underwent TA biopsy were included for analysis based on their respective biopsy results and histopathological diagnoses. Out of these, 8/35 (22.9%) had histopathological findings consistent with GCA (with typical features of active arteritis in 7/8 and one (1/8) burnt-out case). The remaining 27/35 (77.1%) biopsies did not confirm the diagnosis of GCA and were either histologically unremarkable in 12/35 (34.3%) or consistent with atherosclerosis in 15/35 (42.9%). The results of this study have been reported for the entire patient group, for the positive biopsies, and the negative biopsies, respectively. Two sets of analysis results were performed, one to compare the two originally defined groups of eight biopsy-positive patients to the 27 biopsy-negative, and the second to compare the eight biopsy-positive cases to the 15 atherosclerotic cases, excluding patients with normal TA biopsy.

3.1 Demographic Results

The mean age of all patients was 66 ± 10.9 years. Slightly more than half (19/35) were females (54.3%). The remaining 16/35 were males (45.7%). In regards to nationality, 97.1% (34/35) of patients were Saudis and 2.9% (1/35) were non-Saudis. Out of all Saudi patients (34), 52.9% (18/34) originated from the Central province of the country.

In the group with positive TA biopsies, the mean age of patients was 71 ± 8.4 years with a higher female predominance in 62.5% of the cases and a female-to-male ratio of 5:3. The patients in this group were all Saudi nationals. In the group with negative TA biopsies, the mean age was 65 ± 11.2 years with almost equal gender distribution: 14/27 females (51.9%) and 13/27 males (48.1%). Non-Saudis constituted 3.7% (1/27) of the patients.

3.2 Histopathology

The TA biopsies were all grossly examined with measurements of the temporal artery dimensions (length and diameter). All biopsies measured 2.0 cm or more in length and were serially sectioned and submitted "en toto." In 7/8 of the positive cases, the TA showed typical interrupted internal elastic lamina with

granulomatous reaction in the same areas of interruption defined as a collection of histiocytes with formation of variable numbers of giant cells (Figures 1A, B). Secondary findings included narrowing of or occluded lumen with thickened intima and minor degenerative changes in the media. In addition, a similar granulomatous reaction was observed within the adventitia in the remaining burnt-out case (1/8). The interruption of the internal elastic lamina was nicely demonstrated using elastin stain (Figures 1C, D). In contrast, 15/27 of the negative biopsies (55.6%) displayed atherosclerotic changes with narrowing of the lumen, thickened intima, atrophy of the media, and calcific plaques. The remaining 12/27 (44.4%) demonstrated histologically unremarkable TA biopsies.

3.3 Clinical results

The clinical/diagnostic score we have adopted from the ACR/EULAR criteria was utilized to assign each patient a clinical score. In the eight patients with positive GCA on histopathology, scores ranged from five to 12, with a mean value of 7.5 ± 2.33, as opposed to a mean of 4.85 ± 2.01 in patients with GCA-negative biopsies (p-value = 0.003). The variables used to calculate this score as well as additional clinical signs and symptoms are summarized in Table 1, with a calculated level of statistical significance for each. The clinical features that were found to be significantly more common in the GCA biopsy-positive group were scalp tenderness and optic nerve (ON) pallor (p = 0.001 and p = 0.039, respectively). Moreover, the p-value for jaw and/or tongue claudication was found to be close to statical significance (p = 0.067) and thus, was re-assessed by comparing the eight GCA-positive patients to the 12 patients with normal TA biopsy findings (excluding the ones with atherosclerosis). As a result, this variable was found to be statistically significant with p = 0.049.

Regarding the lab results, elevated ESR (≥50 mm/hr) was seen in 7/8 (87.5%) and 22/27 (81.5%) of GCA-positive and GCA-negative cases, respectively.

Similar observations and statistically significant differences were found when comparing the eight GCA-positive patients and the 15 patients with atherosclerotic changes on TA biopsy (summarized in Table 2) in terms of the adopted clinical score, the presentation with scalp tenderness, and the presence of ON pallor on fundoscopic examination (p values of 0.022, 0.006, and 0.023 respectively).

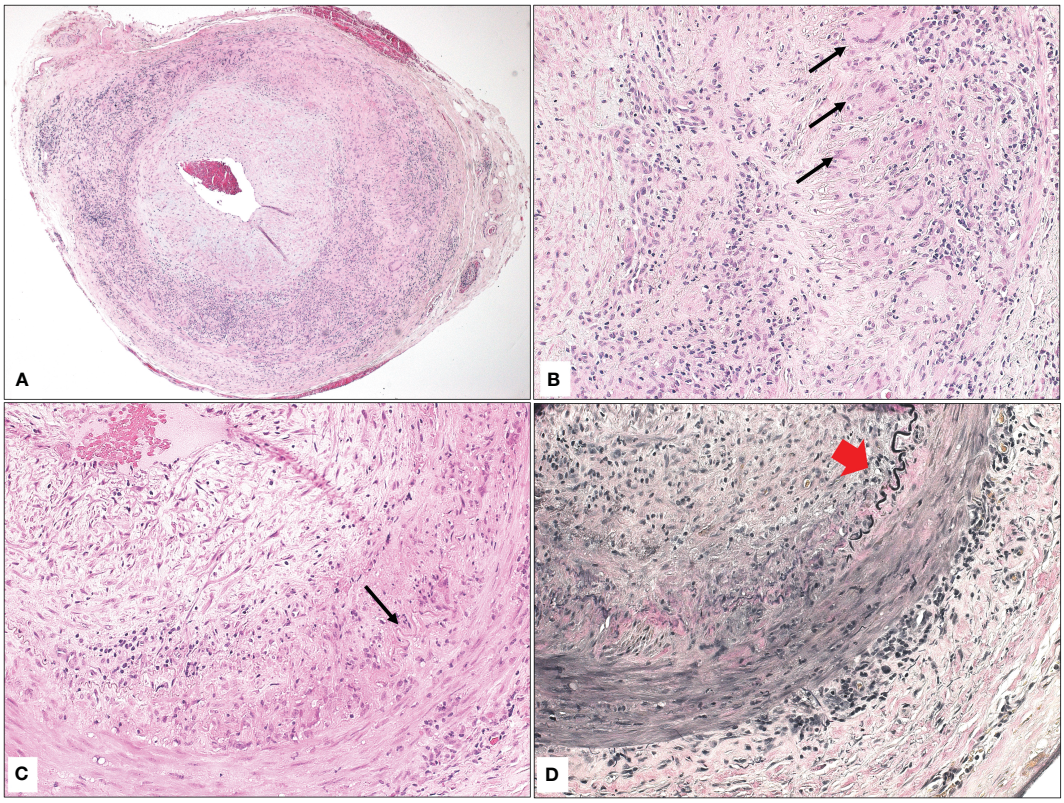

FIGURE 1
(A) The histopathological appearance of a temporal artery with narrowed lumen, atrophic media, interrupted elastic lamina, and granulomatous inflammation consistent with the diagnosis of giant cell arteritis (Original magnification x 50 Hematoxylin & eosin). **(B)** Higher power of the typical area of granulomatous inflammation with multiple giant cells (black arrows) in the area of interrupted elastic lamina (Original magnification x 400 Hematoxylin & eosin). **(C)** Similar findings in another temporal artery biopsy with interrupted elastic lamina (black arrow), granulomatous inflammation, and giant cell formation (Original magnification x 200 Hematoxylin & eosin). **(D)** The area of interrupted elastic lamina (red arrowhead) is clearer now after special staining (Original magnification x 200 Elastin).

TABLE 2 Comparison between the biopsy-positive and atherosclerotic changes groups.

Variables		Biopsy Results				*p* (<0.05)
		GCA Positive (n = 8)		Atherosclerotic Changes (n= 15)		
		Frequency	%	Frequency	%	
Components of Diagnostic Score	Sudden visual loss	8	100	14	93.3	>0.999
	New temporal headache	5	62.5	10	66.7	>0.999
	Jaw or tongue claudication	3	37.5	2	13.3	0.297
	Morning stiffness in shoulders and/or neck	1	12.5	1	6.7	>0.999
	Scalp tenderness	7	87.5	3	20.0	**0.006**
	Abnormal temporal exam	2	25.0	2	13.3	0.589
Corresponding Diagnostic Score (mean ± SD)*		7.5 ± 2.33		5.13 ± 2.10		**0.022**
Neck pain		2	25.0	1	6.7	0.269
Sweats		0	0.0	3	20.0	0.526
Generalized weakness		2	25.0	2	13.3	0.589
Optic nerve changes		6	75.0	10	66.7	>0.999
Optic nerve pallor		6	75.0	3	20.0	**0.023**
Elevated ESR (≥50 mm/hr)		7	87.5	14	93.3	>0.999

GCA, Giant cell arteritis. * Defined as all of the items mentioned above the score (i.e., sudden visual loss, new temporal headache, jaw or tongue claudication, morning stiffness in shoulders and/or neck, scalp tenderness, abnormal temporal artery exam).
Bold values are statistically significant P values.

4 Discussion

Temporal artery (TA) biopsy remains a chief diagnostic tool for GCA. However, its relatively invasive nature and variable sensitivity make its routine implementation difficult (6). Therefore, unnecessary TA biopsies can be avoided with the usage of clinically oriented diagnostic tools. In Saudi Arabia, GCA has been found to be consistently of low incidence, not unlike other Middle Eastern and Mediterranean countries (7). A prior retrospective analysis conducted at KKESH, found that 6.8% (7/102) of patients who underwent TA biopsy between 1983 – 2004, had biopsy-positive GCA (8). In our study, a higher proportion of biopsies (22.9%) performed over 23 years (2000 – 2023) conveyed positive GCA on histological exam. Kaltsonoudis et al. similarly described that only 20% of TA biopsies performed at their institution over 17 years (2000 – 2017) were positive for GCA (9). We still believe that the number of negative biopsies at our institution is relatively high and consequently, some of these biopsies may be considered unjustifiable. This emphasizes the need for better clinical assessment before the TA biopsy is performed.

Almost all patients with GCA biopsy-positive (7/8) had typical active arteritis findings on histopathological examination, affecting all layers of the arterial wall with one burnt-out case with residual typical granulomatous arteritis involving the adventitia. Hernández-Rodríguez et al. reported that biopsies with more extensive infiltration into the arterial wall were increasingly associated with jaw claudication and scalp tenderness, in contrast to those with exclusive adventitial involvement (10). Owing to the small number of biopsy-positive cases in this study, such correlation is not expected to be reliable. However, while there were appreciable differences between the frequency of presenting clinical signs, scalp tenderness was the most important sign with a statistically significant difference between biopsy-positive and biopsy-negative groups (p = 0.001), and between the biopsy-positive and atherosclerosis group (p = 0.006). Molina-Collada et al. and van Nieuwland et al. both reported similar findings in their respective investigations, highlighting the importance of this sign in clinical assessment (11, 12). To add, new-onset jaw claudication is one of the most common symptoms reported by GCA patients (13). In our study, jaw claudication was seen in 3/8 (37.5%) of biopsy-positive patients versus 2/27 (7.4%) of biopsy-negative patients. Even though the p-value (p = 0.067) was not statistically significant between the two groups, one must keep in mind that the GCA-negative group included normal TA biopsies as well as TA biopsies showing atherosclerosis. Therefore, upon recalculation of the p value by comparing the eight GCA-positive cases to the 12 cases with normal TA biopsy (excluding atherosclerotic TA biopsies), statistical significance was found with p = 0.049 as per the footnote in Table 1. Thus, there is increasing evidence to believe that jaw claudication is an important sign with the more evenly assigned grouping. Lecler et al. demonstrated a more evenly assigned patient grouping, with 25 GCA-positive and 20 GCA-negative patients. In their study, jaw claudication showed an even higher statistical significance of p = 0.001, occurring in 64% of GCA-positive patients while none of the GCA-negative patients showed such a sign (14). Similarly, none of our patients with normal TA biopsies experienced jaw claudication. Our conclusion is further supported

since the presence of this sign was not found to be statistically significant when comparing the eight GCA-positive patients to the 15 patients in the atherosclerosis group alone, as seen in Table 2.

Regarding the presenting symptoms, it has been reported that visual disturbances, most commonly sudden visual loss, are a hallmark of giant cell arteritis (8, 9, 15). In our study, all biopsy-positive patients experienced some degree of subjective sudden visual loss as opposed to the 85.2% (23/27) of biopsy-negative patients. However, since our study was conducted in an eye tertiary care center, where patients are referred mostly for visual disturbances, the biopsy-negative group will include patients who have experienced visual loss due to other causes. These patients have been likely referred to the center mainly because of their visual symptoms rather than a constellation of systemic symptoms consistent with GCA (8).

GCA's inflammatory nature may trigger the occlusion of orbital arteries, causing optic nerve pallor (16). The arteritic ischemic optic neuropathy that develops in GCA has been proven to manifest acutely as optic nerve pallor, illustrating fundoscopy's vital nature in the diagnosis of patients with potential GCA (17). On fundoscopy, ON pallor was one of the presenting signs showing statistical significance in the two previously mentioned comparisons illustrated in Tables 1, 2 with p-values of 0.039 and 0.023, respectively.

According to the ACR/EULAR classification criteria for GCA, a score of ≥6 must be obtained for the diagnosis of GCA (5). This can be achieved with or without a positive TA biopsy. The diagnostic clinical score used in our analysis only incorporates the clinical aspects of the ACR/EULAR criteria i.e., the presenting signs and symptoms. The average scores for the biopsy-positive and biopsy-negative groups were 7.5 ± 2.33 and 4.85 ± 2.01 (p = 0.003), respectively. This implies that those who were GCA-positive, on average, could have been theoretically diagnosed with GCA based purely on clinical findings as per the above statistically significant difference.

However, keeping in line with the ACR/EULAR considerations, the criteria may only be applied when: a diagnosis of medium or large-vessel vasculitis has been made, when alternate mimickers have been excluded, and finally if the patient's age was ≥ 50 years at the time of diagnosis as an absolute criterion (5, 18). In our cohort, we have observed an age range of 46 - 93 years, which indicates that the ACR/EULAR considerations for TA biopsy were not strictly followed. When we compared this age range to the corresponding age range in the group of patients with biopsy-confirmed GCA (60 – 81 years), one can conclude that applying the cut-off age of ≥ 50 years for consideration of GCA is reasonable. In addition, the importance of a full clinical exam before any invasive diagnostic measure, i.e., TA biopsy, cannot be understated. Multiple authors have suggested employing clinical algorithms to improve diagnostic protocol (19–21). Some preliminary algorithm models suggest that GCA diagnosis can be achieved through a combination of demographic information, a detailed history, physical exam, and fundoscopic findings (20). We highly recommend developing such an algorithm with stronger consideration for age and clinical manifestations before the performance of a TA biopsy.

Regarding the laboratory investigations, ESR is known to be increased in GCA (15). However, when this parameter was tested in our study, the difference among the analyzed groups (Tables 1, 2) was not statistically significant.

Further efforts to avoid the invasive TA biopsy have been advocated. There is mounting evidence that Doppler ultrasound, as well as magnetic resonance imaging (MRI) or positron emission tomography (PET) scans, should be increasingly utilized in GCA diagnosis (6, 22, 23). Ultrasounds have been shown to have increased sensitivity in detecting GCA in comparison to TA biopsy (6). Thus, the use of ultrasounds may decrease the burden of TA biopsy in various communities, due to an earlier and less invasive diagnosis of GCA. The Rheumatology Spanish Society in their multicenter arteritis study have demonstrated the changes in the diagnostic trends in cases of GCA following the EULAR recommendations (23). Ultrasound use has been increasingly used as a first diagnostic tool in about 53% followed by TA biopsy in 33% then PET scans in 19.6% (23). They also mentioned the impact of the variability in imaging machines and Ultrasonographer' experience. To our knowledge, none of the patients in this study underwent such imaging, possibly because our Ultrasonographers, who were mainly trained to perform ocular Biomicroscopy, did not have the capacity to perform non-ocular ultrasound studies. Others have advocated the use of MRI as a first imaging tool in their most accurate GCA diagnostic algorithm followed by either US or retinal angiography (14).

Limitations of this study include the small study sample of TA biopsies, where only a small number of patients over several years could have been clinically analyzed retrospectively. This might be related to the relative rarity of GCA in our region of the world, taking into consideration that KKESH is a major referral tertiary eye care center. Despite that, our findings have highlighted important clinical features of GCA that will help guide ophthalmologists to attain better ophthalmic practice when dealing with suspected GCA cases. The sample size for the cases with atherosclerotic changes was even smaller since we only receive the group of these patients who are referred to our eye center or seek ophthalmic consultations because of visual disturbance. Therefore, conducting similar future study in collaboration with a general hospital to recruit higher number of patients in that category and compare their findings to GCA cases would be also beneficial.

5 Conclusions

TA biopsy is commonly used for the diagnosis of GCA. However, the incorporation of a unified criteria, targeted history taking, a full head and neck examination, and fundoscopic assessment with certain clinical considerations, can increase the diagnostic accuracy of GCA. It is highly unlikely that biopsies will be rendered completely obsolete but unnecessary biopsies can be avoided by using the ACR/EULAR criteria as a guide. We highly recommend applying the cut-off age of ≥ 50 years as an initial step, followed by the consideration of the following significant clinical features: scalp tenderness, jaw claudication, and ON pallor.

Generally, the incorporation of increased clinically focused assessments, imaging techniques, and algorithms, including the clinical scoring that we have extracted from the ACR/EULAR criteria, may decrease the frequency of TA biopsies and prevent unnecessary costs of this procedure. We also advocate performing future prospective multi-center population-based studies on GCA in this part of the world.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Human Ethics Committee/Institutional Review Board at King Khaled Eye Specialist Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from tissue samples that were obtained for diagnostic purpose then included in this retrospective study with expedited approval of the research project. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

HA: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. FA: Data curation, Writing – original draft. AM: Investigation, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fopht.2023.1327420/full#supplementary-material

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Emerging therapies in the medical management of thyroid eye disease

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Introduction: Thyroid eye disease (TED) is an immune-mediated disorder associated with a heterogenous array of manifestations that may unfavorably impact vision and quality of life. As understanding of this entity's complex pathogenesis has evolved, so have therapies with novel molecular targets offering promise for improved patient outcomes.

Results: Emerging immunologic therapies for the management of thyroid eye disease have diverse mechanisms of actions and routes of administration. Different conventional and biological immunosuppressive agents have been studied as mediators of the autoimmune and autoinflammatory pathways in thyroid eye disease. Teprotumumab – an anti-IGF-1R monoclonal antibody that has recently emerged as a first-line therapy for active, moderate-to-severe TED – has demonstrated statistically significant improvements in proptosis, diplopia, clinical activity score, and quality of life compared to placebo. Currently under investigation are several other agents, with varying administration modalities, that aim to inhibit IGF-1R: VRDN-001 (intravenous), VRDN-002 or VRDN-003 (subcutaneous), lonigutamab (subcutaneous), and linsitinib (oral). Tocilizumab, a monoclonal antibody of interleukin 6, has played a role in the management of multiple autoimmune and inflammatory conditions and may offer promise in TED. Another incipient biologic target for TED management is the neonatal Fc receptor, inhibition of which has potential to decrease recycling of immunoglobulin and antibody levels; agents addressing this target including monoclonal antibodies as well as antibody fragments. Finally, hypolipidemic agents may play a role as mediators of TED-associated inflammation.

Conclusion: Among the agents under investigation that aim to decrease ocular morbidity associated with TED are agents that IGF-1R, interleukin 6, and the neonatal Fc receptor. The management of TED continues to expand with novel immunologic approaches for disease therapy.

KEYWORDS

thyroid eye disease (TED), teprotumumab, Graves' disease (GD), thyroid orbitopathy, neonatal Fc receptor (FcRn), IGF-1R

Introduction

Thyroid eye disease (TED) is a multifactorial autoimmune disorder with an annual incidence of 20-50 cases per 100,000 individuals (1). While this entity most commonly occurs among individuals with Graves' hyperthyroidism, it may also afflict persons with Hashimoto thyroiditis (immune-induced hypothyroidism) as well as those with normal thyroid function. In addition, genetics, immune status, and environmental factors such as smoking and stress play a role in disease pathogenesis.

Thyroid eye disease is associated with a heterogenous array of clinical findings secondary to orbital fibroblast activation and consequent connective tissue remodeling, orbital fat expansion, and extraocular muscle enlargement. The most frequently reported sign of TED is upper eyelid retraction, while additional disease features include proptosis, lagophthalmos, restrictive strabismus, surface keratopathy, and optic nerve dysfunction (2). Appropriate evaluation of these diverse clinical phenotypes may require a multidisciplinary team consisting of endocrinology, neuro-ophthalmology, adult strabismus, and oculoplastic surgery.

Management of thyroid eye disease

Management of endocrine disease may require antithyroid medication, radioactive iodine ablation, or thyroidectomy. Albeit regulation of thyroid function is imperative among TED patients, the course and severity of ocular manifestations are relatively asynchronous to those of the comorbid endocrine dysfunction.

Management of TED is multifaceted, and is determined based on clinical activity, progression, and associated morbidity. In addition to supportive measures (i.e., lubrication, prism therapy, selenium supplementation, and smoking cessation), the historical mainstays of non-surgical therapy to address orbital inflammation were high-dose glucocorticoids and orbital radiation; surgical management plays an integral role in addressing associated orbital, motility, and eyelid pathology, but is beyond the scope of this review.

Emerging immunologic therapies for the management of thyroid eye disease have diverse mechanisms of actions and routes of administration (3–5). Different conventional and biological immunosuppressive agents, such as cyclosporine, mycophenolate mofetil, rituximab, have been studied as a mediator of the autoimmune and autoinflammatory pathways in thyroid eye disease. As understanding of the complex pathogenesis of TED has evolved, so too have medical therapies with novel molecular targets offering promise for improved patient outcomes.

Targets of emerging therapies

Thyroid stimulating hormone receptor and insulin-like growth factor 1 receptor

Thyroid stimulating hormone receptor (TSHR) – a guanine nucleotide-binding protein-coupled seven-transmembrane-domain receptor – is an autoantigen shared by the thyroid gland and the orbit (6, 7). In TED, activation of T cells sensitized to this receptor fosters release of TSHR autoantibodies, which mediate secretion of excess thyroid hormone by the thyroid gland and bind to TSHR expressed by fibroblasts in the orbit. Activation of the TSHR and insulin-like growth factor 1 receptor (IGF-1R) – a transmembrane tyrosine kinase-containing receptor – complex on orbital fibroblasts and functional crosstalk between these two entities triggers an inflammatory cascade, culminating in cytokine and chemokine release, hyaluronan synthesis, and adipogenesis (8).

Teprotumumab

Teprotumumab – a fully human monoclonal antibody that binds to the extracellular alpha subunit of IGF-1R – was developed originally as an antineoplastic agent for solid and hematologic tumors and subsequently investigated as a target for the management of TED. This IGF-1R antagonist decreases IGF-R1 and TSHR display on fibrocytes, inhibits Akt phosphorylation, and inhibits the induction of pro-inflammatory cytokines (9). The encumbrance by teprotumumab of pathways crucial to muscle cell and adipocyte integrity leads to downstream impacts on extraocular muscle an orbital fat composition and volume.

Two consecutive, multicenter, randomized, double-masked, placebo-controlled clinical trials (ClinicalTrials.gov Identifiers: NCT01868997 and NCT03298867, also known as OPTIC) among patients with active, recent-onset, moderate-to-severe TED demonstrated statistically significant, sustained improvements in proptosis, clinical activity score, diplopia, and quality of life with teprotumumab therapy as compared to placebo (10, 11). On the basis of these investigations, teprotumumab was approved by the United States Food and Drug Administration in January 2020 for the management of adults with TED. An open-label clinical extension study (NCT03461211, or OPTIC-X) analyzed the role of teprotumumab therapy among patients who were previously nonresponsive or who experienced a disease flare and demonstrated similar efficacy with regards to primary and secondary outcome measures as compared to its namesake study (12). The results from OPTIC-X demonstrated that while relapse rates following teprotumumab therapy are non-negligible, patients with a history of insufficient response or flare may benefit from additional therapy; moreover, duration of TED may not serve as a significant predictive indicator for response to teprotumumab therapy. Among patients with chronic, stable TED, teprotumumab has also shown promise for reductions in proptosis, diplopia, and extraocular muscle and orbital fat volume (13–15).

Teprotumumab is typically administered over 60 to 90 minutes as a total of 8 intravenous infusions, completed every three weeks (16). The standard medication dose is 10 mg/kg of body weight for the first infusion followed by 20 mg/kg of body weight for subsequent infusions. The most frequent adverse effects associated with teprotumumab are muscle spasms (25%), nausea (17%), alopecia (13%), diarrhea (12%), fatigue (12%), hyperglycemia (10%), and hearing impairment (10%) (17). Pre-infusion screening of all patients should include complete medical and ocular examinations, baseline laboratory tests (i.e., complete

blood count, fasting blood glucose, hemoglobin A1C, liver function tests), and baseline electrocardiogram. As a result of recent literature expounding irreversible sensorineural hearing loss linked to teprotumumab therapy, many entities advocate for audiometric testing pre-, intra-, and post-therapy, particularly among individuals with a history of hearing loss (18–20). In addition, contraindications to therapy include current pregnant or nursing status, prepubertal age, and concomitant biologics or recent rituximab use; poorly controlled diabetes and inflammatory bowel disease represent areas of caution and require co-management with endocrinology and gastroenterology, respectively (16).

VRDN-001

VRDN-001, a full antagonist antibody of IGF-1R, was the subject of investigation for a phase ½ randomized, double-masked clinical trial (NCT05176639). According to authors, VRDN-001 inhibited ligand binding and IGF-1 induced IGF-1R and Akt phosphorylation more completely than teprotumumab in the dose range tested. Among patients with chronic TED, an assessment was completed of therapy with either 10 mg/kg or 3 mg/kg of body weight of VRDN-001 for two intravenous infusions, three weeks apart, as compared to placebo. In this study, two infusions led to substantial reductions in proptosis and clinical activity scores. No patients treated with VRDN-001 achieve completed resolution of diplopia at week six. Moreover, there were no reported serious adverse events, including hearing impairment and hyperglycemia. A phase 3 trial (THRIVE) aims to further outline the efficacy and safety of VRDN-001 (21, 22).

Other agents

Currently in the pipeline are several other agents, with varying administration modalities that aim to inhibit IGF-1R. VRDN-002 and -003 are monoclonal antibodies to IGF-1R with half-life extension technology (23–26). Supported by encouraging data from the 3 mg/kg dose cohort of the VRDN-001 study, VRDN-002 and -003 were developed as low volume, monthly administered, subcutaneous agents and may be subjects of further clinical investigation. Lonigutamab is in a phase ½ randomized, double-masked clinical trial (NCT05683496) as another subcutaneous therapy. Finally, linsitinib is the subject of a phase 2b randomized double-masked study (NCT05276063) as twice daily, oral medication for TED (27). An alternative subject of investigation to IGF-1R is TSHR, which serves as the target of human monoclonal autoantibody K1-70; administration of this agent via intramuscular and intravenous routes has been assessed in a phase I clinical trial (Integrated Research Application System Identifier: 199697) (28).

Interleukin 6

Interleukin 6 increases expression of TSHR in orbital fibroblasts, augmenting TSHR autoantibody-mediated stimulation of the fibroblasts (29). Tocilizumab – a humanized recombinant monoclonal antibody of interleukin 6 – has played in the role of the management of multiple autoimmune and inflammatory conditions such as rheumatoid arthritis, giant cell arteritis, and juvenile idiopathic arthritis. In a randomized, double-masked clinical trial assessing the efficacy of intravenous tocilizumab at a dose of 8 mg/kg of body weight, compared to placebo, in patients with steroid-resistant, active, moderate-to-severe TED demonstrated meaningful improvements in clinical activity scores and proptosis (30). Adverse effects linked to this agent include hypercholesterolemia, neutropenia, and transaminitis, though reports of associated adverse effects in TED have been lower than those in other autoimmune conditions (31). A randomized, multicenter clinical trial (NCT04876534) is underway to compare treatment with tocilizumab or methylprednisolone for patients with active, moderate-to-severe TED.

Neonatal fragment crystallizable receptor

The neonatal fragment crystallizable receptor (FcRn) plays a role immunoglobulin G transport across barriers and in its protection from lysosomal degradation (32, 33). Batoclimab – a monoclonal antibody of FcRn – reduces the Fc-Rn-mediated recycling of immunoglobulin G and may promote degradation of pathogenic antibodies against TSHR and IGF-1R. In a phase 2a, multi-center, open-label trial (NCT03922321, or ASCEND-GO 1), seven subjects with active, moderate-to-severe TED received weekly subcutaneous injections of batoclimab, 680 mg for two weeks followed by 340 mg for four weeks (34). Among these patients, levels of serum immunoglobulin G and anti-TSHR antibodies decreased by 64.8% and 56.7%, respectively. Subsequently, batoclimab was assessed for active, moderate-to-severe TED in a phase 2b, randomized, placebo-controlled study (NCT03938545, or ASCEND-GO 2), which was terminated secondary to elevations in serum cholesterol levels among study participants (4). Multiple other anti-FcRn agents, including monoclonal antibodies and antibody fragments, are currently under investigation for a variety of immunoglobulin G-mediated autoimmune conditions, and may be explored as therapeutic targets for TED in the future.

Hydroxymethylglutaryl-coenzyme A reductase

Statins, also known as hydroxymethylglutaryl-coenzyme A reductase inhibitors, are a class of hypolipidemic drugs that have been reported in recent years to also exhibit pleiotropic anti-inflammatory, -fibrotic, and -immunomodulatory behavior (4). In orbital fibroblasts, its therapeutic effect has been attributed to suppression of transforming growth factor beta-induced fibrosis markers, inhibition of tumor necrosis factor alpha-induced pro-inflammatory factors, and downregulation of adipogenesis (35–38). In a recent report, stain users were found to be less likely to develop TED, with a full adjusted hazard ratio of 0.78 for men and 0.91 for women; other lipid-lowering medications did not demonstrate a comparable protective effect (39). In a phase 2, open-label, single

center, randomized clinical trial (NCT03110848, or STAGO), addition of oral atorvastatin to an intravenous glucocorticoid regimen for patients with hypercholesterolemia and active, moderate-to-severe TED demonstrated improvements in orbitopathy outcomes. Additional hypolipidemic agents that have shown early signs of promise as anti-inflammatory vehicles in TED include biguanide hypoglycemic drugs and antibodies against proprotein convertase subtilisin/kexin type 9 (40, 41).

Additional agents

Immunomodulatory agents under study for potential use in the management of TED include: belimumab, a monoclonal anti-serum B cell stimulating factor antibody used in the treatment of systemic lupus erythematous (EU Clinical Trials Identifier: EudraCT 2015–002127–26); secukinumab, a monoclonal anti-interleukin 17A antibody approved for the management of severe plaque psoriasis, psoriatic arthritis, and axial spondyloarthritis (NCT04737330); and aflibercept, a soluble decoy receptor that binds vascular endothelial growth factor-A and -B and placental growth factor (NCT04311606). A diverse array of additional anti-inflammatory targets is currently in the exploratory pipeline for TED therapy, including hydroxychloroquine, sirolimus, tamsulosin, bimatoprost, and doxycycline (3).

Discussion

Thyroid eye disease is a complex, immune-mediated disorder characterized by inflammatory dysregulation and remodeling of the periorbita and orbit. Over the last few decades, significant developments in the understanding of disease pathophysiology have allowed researchers and clinicians to identify and hone novel molecular targets for therapy. Emerging immunologic therapies for the management of thyroid eye disease have diverse mechanisms of actions and routes of administration. Among the agents under investigation that aim to decrease ocular morbidity associated with TED are agents that IGF-1R, interleukin 6, and the neonatal Fc receptor. These novel immunologic approaches for disease therapy show promise for enhanced function, cosmesis, and quality of life among patients with TED.

Future discovery efforts for TED must identify and characterize candidate drugs that optimize both clinical efficacy and patient safety. In order to achieve this well-balanced profile, investigative endeavors titrating drug dose, quantity, frequency, and route are paramount. Moreover, detailed reporting of drug-associated pharmacotoxicity and studies aiming to prevent, minimize, or treat adverse effects of the associated therapies is crucial. Ultimately, case-specific algorithms may be developed that couple known patient demographics, comorbidities, and risk factors with disease activity and severity to refine therapeutic recommendations effectively and safely.

Author contributions

AK: Investigation, Writing – original draft, Writing – review & editing. AH: Writing – review & editing. AM: Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

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Publisher's note

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Clinical utility of square-wave jerks in neurology and psychiatry

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Human eye fixation is steadily interrupted by small, physiological or abnormal, eye movements. Square-wave jerks (SWJ) are the most common saccadic intrusion which can be readily seen at the bedside and also quantified using oculographic techniques. Various neurological, neuropsychiatric and psychiatric disorders display abnormal fixational eye movement patterns characterized by frequent SWJ. For the clinician, SWJ are particularly important because they can be readily observed at the bedside. Here, we will discuss the pathological conditions that present with SWJ and explore the expanding body of literature suggesting that SWJ may serve as a potential indicator for various clinical conditions.

KEYWORDS

square-wave jerks, eye movements, fixation, saccadic intrusions, progressive supranuclear palsy, cerebellar ataxia

1 Introduction

Foveate animals, including humans, can look quietly at a target for prolonged periods of time. This ocular motor condition is called fixation and is based on an active and dynamic eye stabilization system (1). Early on, it became clear that maintained fixation is steadily interrupted by a variety of small, fast and slow, eye displacements (2, 3). Traditionally, these eye movements are divided into two categories: a repertoire of physiological idiosyncratic miniature movements (microsaccades, ocular drift and ocular microtremor) collectively called fixational eye movements (4) and a group of larger, and therefore clinically visible, fixational intrusions comprising SWJ, ocular flutter, opsoclonus, saccadic pulses and macrosaccadic oscillations (5). The distinction of normal fixational eye movements versus abnormal saccadic intrusions, however, might prove to be more of a working hypothesis than an empirical reality. This is particularly true for microsaccades and SWJ, which likely represent different magnitudes across a saccadic continuum extending from fixation to exploration (6). Being easy to assess at the bedside, SWJ are certainly the best-studied saccadic

intrusion. Here, we review the measurement methods of SWJ using quantitative oculography and discuss the various neurological and psychiatric conditions that affect the occurrence of SWJ.

2 Characteristics, recording and quantification of SWJ

SWJ can be defined as a pair of small (<5 deg) saccades, each of them conjugate. The first one moves the eye away from the fixation point, whereas the second one returns the eye toward the target (corrective saccade), after a short time interval (usually less than 300 ms). SWJ seem to have a strong horizontal preference in humans, something that does not apply to non-human foveate animals, which may show a greater vertical predisposition (7). Macro-SWJ display amplitudes of up to 30 deg and are less commonly observed in clinical practice. Bursts or prolonged series of repetitive, nearly continuous disruptions of fixation are categorized as saccadic oscillations. These may manifest either as SWJ-oscillations or as back-to-back saccadic oscillations without intersaccadic intervals. In the latter case, ocular oscillations are classified as opsoclonus or ocular flutter, depending on whether the oscillations occur in all directions or are restricted to the horizontal plane, respectively.

The genesis of SWJ is still uncertain. A dysfunction of a brainstem oculomotor network is assumed, where the inhibition exerted by the inhibitory burst neurons (IBNs) on the omnipause neurons (OPNs) overcomes the inhibition of the OPNs on the IBNs. Subsequently a short burst of activity appears in the excitatory burst neurons that produces a small saccade. In turn, this produces a small retinal error that is detected in the superior colliculus (SC) which results in a second saccade in the opposite direction, completing a SWJ (8). The cerebellum, basal ganglia, and cortical regions are directly and indirectly interconnected within this network, thereby influencing its functionality (9).

In order to detect and quantify SWJ, precise eye position data has to be obtained. Out of various eye tracking methods, two are the most commonly used for these purposes: Magnetic Field/Scleral Search Coil (SSC) and Video-Oculography (VOG). The former, albeit more invasive and not as well tolerated, is considered more precise and accurate than the latter. However, they have both shown adequate performance in detecting saccades of small magnitude. Temporal resolution is highest for SSC (500+ Hz), but high-end VOG systems can reach frequencies of 400 Hz. Other recording methods, such as Infrared Reflection and DC-electrooculography, are no longer widely used for SWJ detection (10).

Experiments typically consist of subjects viewing a small target on a screen and being asked to maintain fixation for 10-120 seconds. The head is restrained by a forehead-chin headrest. Fixation duration, target shape and size, screen-to-cornea distance and other environmental conditions at the time of the experiment (e.g. lighting) may differ according to the goals of the respective study. In order to detect SWJ from large amounts of data, automated and objective algorithms have been developed. A common approach is to first detect all saccades, using methods reliant on eye movement velocity (11). Saccades are then filtered based on amplitude. Subsequently, pairs of consecutive saccades that are separated by an appropriate intersaccadic interval and display approximately opposite directions and similar magnitudes are classified as SWJ (12). Another approach that has been used is the creation of an SWJ index, incorporating the above metrics in a continuous variable between 0 and 1, and then comparing it to the "ideal SWJ". Index values above a specified threshold are considered to be SWJ (7).

3 SWJ in neurological and psychiatric disorders

3.1 SWJ in cerebellar, brainstem and basal ganglia disorders

Progressive supranuclear palsy (PSP) and cerebellar ataxias are perhaps the most widely recognized neurological disorders in which SWJ play a prominent role in their phenotype (Figure 1A). Early on, Troost et al. recognized that SWJ were the second most prevalent ocular motor disorder in PSP after saccadic slowing (14). Subsequently, several clinical and oculographic studies have confirmed and quantified the presence of SWJ in PSP (9, 15–20)]. The occurrence of >10 SWJ/min with amplitudes up to 4 deg, have been recently included in the clinical diagnostic criteria of PSP by the Movement Disorder Society (21). While more prevalent in PSP, SWJ also occur, albeit less consistently, in various other movement disorders (22–28), with Parkinson's disease being the most characteristic among them (9, 29–31).

Among cerebellar disorders, Friedreich's ataxia (FA) is the most thoroughly studied with regard to SWJ (32). Ribaï et al. followed 37 FA patients prospectively for 7 years using eye movement recordings. These authors found a high frequency of SWJ in all of them at the beginning of the study, with a further increased rate at the end of it (33). In 2008, Fahey et al. investigated SWJ in 15 Friedreich's ataxia (FA) patients under target-on and target-off conditions. They observed longer and larger SWJ in the target-off condition. Younger patients exhibited more fixation instability with more frequent and shorter SWJ in both conditions; no differences in the total number of SWJ between ambulant and non-ambulant participants were found, but the latter group exhibited significantly more macro-SWJ. Interestingly, in almost half of the patients, oblique SWJ with a prominent vertical component, as well as occasional pure vertical SWJ, were recorded (34).

SWJ have been described in many spinocerebellar ataxias (SCA), including SCA1, SCA2, SCA8, SCA10, SCA14, SCA20, SCA21, SCA25, SCA27, SCA29, SCA37, SCA46, and DRLPA, although they are more noticeable in SCA3 and SCA6 (35, 36). Bürk et al. detected SWJ in 30% of SCA3 patients (37), whereas another study reported a percentage of approximately 55% for SCA3 patients; SCA1, SCA2, and SCA6 percentages were found lower, around 20% (38). Similarly, Moscovich et al. found SWJ in 23% of SCA3 patients and 17% of SCA6 patients (39). In 2017, Wu et al. investigated ocular movements in SCA3 and found a high frequency of SWJ in both symptomatic patients (n=44) and SCA3

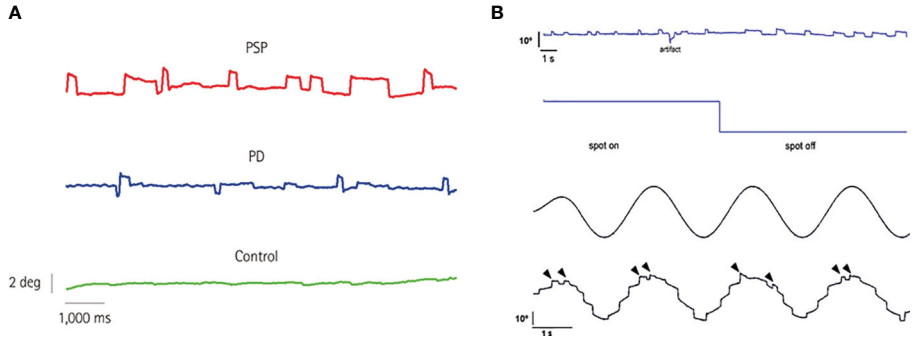

FIGURE 1
(A) Eye position while fixating an LED straight ahead for 10 s in three subjects of the same age (69 years): a PSP patient, a PD patient, and a control subject. Note the increased rate of square-wave jerks in the PSP patient. PD, Parkinson's disease; PSP, progressive supranuclear palsy. From Anagnostou et al. (9), with permission by the "Korean Neurological Association". This figure is published in "Anagnostou E, Karavasilis E, Potiri I, Constantinides V, Efstathopoulos E, Kapaki E, Potagas C. A Cortical Substrate for Square-Wave Jerks in Progressive Supranuclear Palsy. J Clin Neurol 2020;16: 37-45", Copyright Korean Neurological Association. **(B)** 60-year-old man with Langerhans' cell histiocytosis and cerebellar involvement. Continuous SWJ during straight ahead fixation as well as after removal of visual fixation (upper panel). The average frequency of occurrence was 40.8 min^{-1} and remained unchanged after turning the fixation spot off. In the latter case, however, prolonged off-center fixation periods were demonstrated making square-wave intrusions appear wider. Typical pathological staircase appearance of smooth eye tracking in the same subject due to numerous catch-up saccades (lower panel). Notably, SWJ continue to occur during smooth pursuit (arrowheads). From Anagnostou et al. (13), with permission by "Elsevier". This figure is published in "Anagnostou E, Papageorgiou SG, Potagas C, Alexakis T, Kalfakis N, Anastasopoulos D. Square-wave jerks and smooth pursuit impairment as subtle early signs of brain involvement in Langerhans' cell histiocytosis. Clin Neurol Neurosurg 2008;110: 286-290.", Copyright Elsevier.

carriers (n=12) (40). Additionally, Bour et al. recorded downbeat nystagmus accompanied by horizontal SWJ (bow-tie nystagmus) in the majority of SCA6 patients they recruited (n=4/6). Similar oculomotor findings (bow-tie nystagmus) were also observed in patients with familial cortical myoclonic tremor with epilepsy (FCMTE) (n=4/6) (41).

SWJ along with gaze-evoked and/or spontaneous nystagmus are common features of Ataxia-Telangiectasia (42). High SWJ frequency and amplitude have been also found in patients with Ataxia with Oculomotor apraxia type 2 (43). Pronounced oculomotor abnormalities with frequent SWJ have been observed in patients with chorea-acanthocytosis, who have heterozygous VPS13A mutations and basal ganglia degeneration, when compared to normal controls (25). Likewise, SWJ have been reported in adult-onset Alexander disease (44) and X-linked ataxia (45).

Paraneoplastic cerebellar degeneration is associated with a frequent occurrence of SWJ as described in cases of anti-Hu and anti-CV2/CRMP5 cerebellar ataxia associated with Small-Cell Lung Cancer (SCLC) (46, 47). Additionally, SWJ are observed in paraneoplastic Stiff-person syndrome with anti-amphiphysin antibodies, which can be linked to malignancies like SCLC, breast cancer, and Hodgkin's Lymphoma (47). Similarly, frequent SWJ can be found in cerebellar ataxia due to autoimmune mechanisms, whether or not autoantibodies are detected in serum or cerebrospinal fluid (CSF). This includes conditions like anti-GAD Stiff-person syndrome (47) or anti-Sj/ITPR1 and anti-NMDA cerebellar ataxia (48). High frequency SWJ ("square wave oscillations") have been reported in a case of anti-GAD cerebellar ataxia accompanied by autoimmune thyroiditis (49). They have also been described in a patient with steroid-responsive encephalopathy with autoimmune thyroiditis presenting with pure cerebellar ataxia (50) and in a case of a SCLC patient with pembrolizumab therapy-induced encephalitis (51).

A high occurrence of SWJs was found in a case of Langerhans' cell histiocytosis (LCH) with central nervous system involvement (13) (Figure 1B) and has also been described in Creutzfeldt-Jacob disease, presenting with progressive cerebellar ataxia, oculomotor abnormalities, mental impairment and hyper-intensities in the basal ganglia and thalami (52). In Arnold-Chiari malformation type 1, SWJ along with downbeat nystagmus have been described, but only after strabismus surgery (53). In contrast, Chiari type 2 malformation is not associated with an increased SWJ rate (54).

Finally, oculomotor recordings in patients with essential tremor have revealed an increased rate of SWJs, along with increased saccade latency and decreased saccade peak velocity when compared with normal controls. These findings appear to be unrelated to the duration, severity, or treatment of the disease (55).

3.2 SWJ in dementias

It has long been reported that SWJ occur in patients with acute or chronic focal cerebral lesions, regardless of the lesion's location. The amplitude of these SWJ is typically lower than that observed in cerebellar diseases (56).

Typically, SWJ are generated during visual fixation (VF) and suppressed in darkness. However, in Alzheimer's disease (AD), SWJ occur more frequently in low-light conditions than during VF. These SWJ without VF are associated with increased cortical dysfunction (57).

Nonetheless, it has been reported that patients with AD and control subjects do not differ in the rate of intrusive saccades during VF at baseline. Only AD patients exhibit a progressive increase over

an 18-month follow-up period, and this increase correlates with heightened dementia severity. However, it is not specified whether this phenomenon holds true for SWJ, which are paired intrusive saccades characterized by equal amplitude and opposite direction (58).

In another publication, healthy controls and young onset Alzheimer's disease patients (YOAD) also showed no significant difference in the average number of SWJ. However, YOAD patients exhibited a higher frequency of large intrusive saccades and had shorter periods of fixation compared to healthy controls (59).

A slightly different scenario is presented in a study by Shakespeare et al. (60). Patients with typical AD demonstrated an elevated rate of SWJ during attempted VF in comparison to healthy controls. Furthermore, the SWJ rate was found to be associated with a decrease in cerebellar grey matter volume. On the other hand, patients with posterior cortical atrophy, a variant of AD, exhibited increased occurrence of large unpaired saccadic intrusions, which correlated with reduction in cortical thickness.

Small SWJ are defined as paired microsaccades with equal amplitude and opposite directions. Microsaccades in individuals with AD or mild cognitive impairment tend to exhibit a more oblique trajectory when compared to those in healthy controls (61). A high frequency of small SWJ has also been observed in the behavioral variant frontotemporal dementia group compared to age-matched controls. Neural correlates were identified in the orbitofrontal and ventromedial prefrontal cortices, as well as the striatum.

3.3 SWJ in psychiatry

Eye movement studies in psychiatric diseases are more sparse then those in neurologic disorders. Impairments in different oculomotor paradigms have been reported in major depressive disorder (MDD) (62, 63), in bipolar disorder (BD) (62, 64), in obsessive compulsive disorder (OCD) (65), in anorexia nervosa (AN) (66) and especially in schizophrenia (SCZ) (67–69) with some researchers considering them as potential biomarkers (63, 70–72) while others remain more skeptical (68, 73).

SWJ in psychiatric diseases, however, have been less frequently studied, and this not always in dedicated visual fixation paradigms. Regarding SCZ most of the studies have found no differences between SCZ patients and health controls (HC) (67, 74–78). However, one study (79) reported increased frequency in SWJ during smooth pursuit eye movements, while others have even reported lower SWJ rates in patients (80, 81). Clearly, differences in methodological approaches account for these discrepancies. More recently, Levy et al. reported that SWJ frequency was one of the variables that discriminated between subjects with normal and subjects with abnormal smooth pursuit performance (in a mixed group of HC and schizophrenic patients). Hence, the presence of another ocular motor dysfunction (i.e. smooth pursuit) rather than SCZ itself appears critical with respect to the occurrence of SWJ (82).

Data on SWJ in affective disorders are not less contradictory. Sweeney et al. found that patients with BD presented higher rates of SWJ compared to SCZ patients but had no differences compared to controls (81). Flechtner et al. compared the number of SWJ produced by SCZ patients, patients with affective disorders (both MDD and BP) and controls in a smooth pursuit paradigm and reported a trend for patients with affective disorders to perform more SWJ (77). On the other hand, Friedman et al. did not spot any differences between SCZ patients, patients with affective disorders and controls (76, 80). Finally, Sweeney et al. reported increased SWJ rates in MDD patients using a visual fixation task in contrast to the previous studies (83).

Concerning patients with OCD, Sweeney et al. reported increased frequency of SWJ during a smooth pursuit task (84). On the contrary, other studies (85–87) found no increase in the frequency of SWJ in OCD patients compared to controls. Moreover, Pallanti et al. observed SWJ in three anorectic patients while they were absent in controls (88). In a study by Phillipou et al. it was shown that AN patients made SWJ at a higher rate compared to controls which was also negatively correlated with anxiety. Also, 87.7% of AN subjects and 95.5% of healthy participants were properly classified based on SWJ and anxiety scores (89).

4 Discussion

Square Wave Jerks (SWJ) are an especially valuable ocular motor sign due to their ease of detection during bedside physical examinations. However, they often go unnoticed and receive far less attention compared to larger eye movements like saccades and smooth pursuit among general neurologists.

Dedicated studies on SWJ are still relatively scarce, but accumulating evidence underscores their significant relevance in the ocular motor characteristics of movement disorders and cerebellar ataxias. Certainly, PSP and cerebellar syndromes of various etiologies (degenerative, autoimmune, paraneoplastic) stand out as the most extensively studied and well-established central nervous system disorders associated with saccadic intrusions. When it comes to neurodegenerative dementias, there exist somewhat conflicting results. Most studies focus on patients with AD, with some demonstrating an increase in SWJ rates compared to age-matched controls, while others show normal rates. Clearly, methodological variations and, more importantly, diagnostic uncertainties may account for these discrepancies. The inclusion of more homogeneous diagnostic groups based on cerebrospinal fluid biomarkers rather than relying solely on the neuropsychological profile might enable more robust conclusions regarding the role of SWJ in dementia. The same applies to psychiatric disorders, where the concept of drug naivety may be of particular importance in designing methodologically robust studies.

Many clinicians consider SWJ to be rather nonspecific, as they can occur in otherwise healthy elderly individuals, particularly when the rest of the oculomotor examination is normal. The number of SWJ per minute might therefore be a critical parameter given the fact that the occurrence of SWJs is not a binary on-off phenomenon distinguishing health from disease but rather a continuum. To establish a valid clinical criterion, thresholding, particularly in terms of SWJ frequency, is essential. Table 1 offers an overview of SWJ rates as reported in the available literature. Only studies that

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TABLE 1 Summary table of SWJ rates in neurological and psychiatric disorders.

Disorder	Study	Diagnosis	No. of Patients	Mean SWJ rate (SWJ/min)
Brainstem/Cerebellar/ Basal Ganglia	Rascol et al. (15),	PSP	7	54
	Otero-Millan et al. (8),	PSP	10	48
	Anagnostou et al. (9),	PSP	20	33.5 (fixation on) 22.5 (fixation off)
	Pagonabarraga et al. (19),	PSP	65	22.8
	Becker et al., (20)	PSP	50	31.2
	White et al. (29),	PD	14	52
	Rascol et al. (15),	PD	13	45
	Anagnostou et al. (9),	PD	12	10.3 (fixation on) 13.3 (fixation off)
	Pagonabarraga et al. (19),	PD	25	1.2
	Bonnet et al. (27),	Ephedrone-induced Parkinsonism	28	6.8
	Ribaï et al. (33),	Friedreich ataxia	37	36 (first assessment) 54 (7 years later)
	Salman et al. (54),	Chiari malformation type 2	21	3.5
	Gitchel et al. (55),	Essential Tremor	60	26.9
	Wu et al. (40),	SCA3	44 patients 12 pre-clinical carriers	47 32
Dementia	Nakamagoe et al. (57),	Alzheimer's Disease	15	10.4 (fixation on) 20 (fixation off)
	Pavisic et al. (59),	Alzheimer's Disease (young onset), Posterior Cortical Atrophy (young onset)	26, 10	6.2, 4.9
	Shakespeare et al. (60),	Alzheimer's Disease, Posterior Cortical Atrophy	17, 20	36, 18.9
	Kapoula et al. (61),	Alzheimer's Disease, Mild Cognitive Impairment	18, 15	2.0, 2.2
	Russell et al., 2021 (90),	Frontotemporal degeneration (behavioral variant)	19	18.4
Psychiatric	Nickoloff et al. (85),	Obsessive-compulsive disorder	8	3.4
	Sweeney et al. (84),	Obsessive-compulsive disorder	17	7.5
	Campion et al. (75),	Schizophrenia	46 (13 drug-naïve, 20 chronic, 13 residual)	12
	Friedman et al. (80),	Schizophrenia, Affectives	23, 16	7.2, 5.0
	Sweeney et al. (81),	Schizophrenia, Bipolar disorder, Major depressive disorder	101, 17, 13	2.8, 7.5, 3.5
	Friedman et al. (76),	Schizophrenia, Affectives	26, 14	19.8, 24.6
	Flechtner et al. (77),	Schizophrenia, Affectives	43, 34	9.6, 14.7
	Levy et al., (82)	Schizophrenia	43	6
	Phillipou et al. (89),	Anorexia nervosa	22	11.8

reported mean SWJ frequencies, which can be converted into rates per minute, were included, while single case reports were excluded.

There are still important questions awaiting answers concerning the neuronal mechanisms that govern fixation in humans. To gain a deeper understanding of the mechanisms underlying saccadic intrusions in neurological and psychiatric disorders, it would be beneficial to perform a more detailed oculographic categorization of SWJ waveforms, considering factors such as amplitude, direction, and intersaccadic intervals. Combining clinical assessments with quantitative oculographic analysis and both structural and functional neuroimaging approaches is expected to provide further insights into the pathophysiology and clinical significance of ocular oscillations in various disease categories.

Author contributions

AZ: Writing – original draft, Writing – review & editing. GA: Writing – original draft, Writing – review & editing. IS: Writing – original draft, Writing – review & editing. ES: Writing – original draft, Writing – review & editing. FA: Writing – original draft, Writing – review & editing. EA: Writing – original draft, Writing – review & editing.

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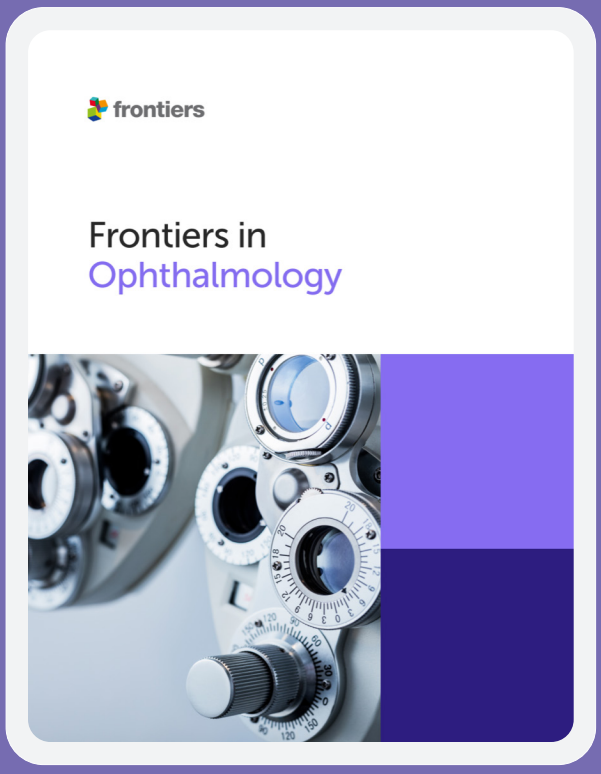

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