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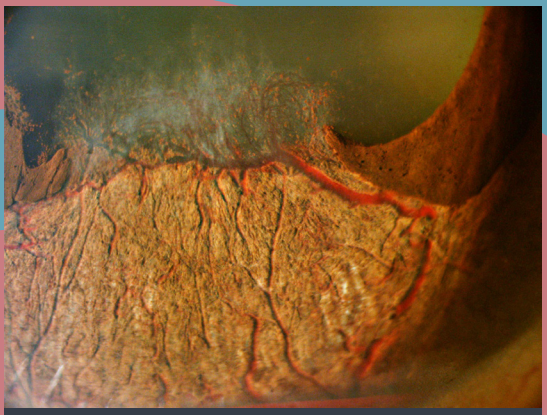

ABOUT THE COVER IMAGE

The volcano is erupting by John Leo from Tun Hussein Onn Eye Hospital, Malaysia. The winner of the photography competition during the 8th Conjoint Ophthalmology Scientific Conference, 14–16 September 2018. The Royale Chulan Hotel, Kuala Lumpur, Malaysia.

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The Malaysian Journal of Ophthalmology (MyJO) is the official journal for the Malaysian Society of Ophthalmology (MSO), College of Ophthalmologists Malaysia, and Malaysian Universities Conjoint Committee in Ophthalmology (MUCCO). MUCCO is the national board responsible for training ophthalmologists in Malaysia, comprising the Universiti Kebangsaan Malaysia, Universiti Malaya, and Universiti Sains Malaysia, as well as the Ministry of Health.

MyJO aims to provide a platform for ophthalmologists, clinicians, researchers, trainees, students, optometrists, and eye care providers to publish their work and to promote knowledge enhancement among ophthalmologists and eye care providers in Malaysia.

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Case reports

IZBA® Launch

Introducing IZBA® (Travoprost 30 microgram/ml) BAK-free Prostaglandin Analog (PGA) - Powerful and sustained IOP lowering with improved safety profile[i,iii]

Saturday
6th October 2018
Hilton KL

Dato' Dr. Linda Teoh Oon Cheng, sharing the challenges in reducing the burden of glaucoma.

As Malaysia's population ages, glaucoma is becoming an increasingly significant cause of blindness. According to the National Eye Survey in 2014, glaucoma is the third leading cause of blindness, contributing to 7% in Malaysia[ii].

Although there are an array of modern therapies, topical glaucoma drops remain the first line treatment due to their high efficacy and good tolerability. As a first-line medication, PGAs offer the highest IOP reduction of 25-35% from baseline[iii]. Other topical agents include beta-blockers (20-25%)[iii], carbonic anhydrase inhibitors (20%)[iii] and alpha-agonists (18-25%)[iii]. Prostaglandin analogues (PGAs) are often preferred because of their IOP-lowering ability, safety profile and once-daily dosing convenience[v].

IZBA® Solution is a new once-daily prostaglandin analogue eye drop indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. IZBA® Solution was launched in Malaysia on October 6, 2018 with **Consultant Ophthalmologists and Glaucoma Specialists Dato' Dr. Linda Teoh from Assunta Hospital and from Taipei Veterans General Hospital, Dr. Chang Yu-Fan.**

IZBA® Solution, containing 0.003% travoprost, offers a similar efficacy to its sibling TRAVATAN® Solution, containing 0.004% travoprost. Sharing her real-world experience with IZBA® in Taiwan, **Dr. Chang Yu-Fan** emphasized that consistent efficacy in treatment will lead to fewer medication switches, improved patient's adherence and optimized cost-effectiveness.

> **Travoprost may be the cost-effective choice as it produces the least percentage difference between peak and trough, and thus the most consistent IOP lowering among available PGAs.**
>
> **- Dr. Chang Yu-Fan**

Dr. Chang Yu-Fan, sharing real-world experience with IZBA® from Taiwan.

The reduced drug concentration found in IZBA® Solution also lowers adverse events and increases patient adherence. IZBA® Solution is less frequently associated with hyperemia, identified as the most common adverse event for patients on PGA therapy. Hyperemia contributes to 63% of adverse event-related stopping or switching of therapy[iv]. An article by Peace and colleagues revealed that only 11.8% of patients treated with IZBA® Solution experienced hyperemia compared to 14.5% of those treated with Travatan® Solution[v] . Furthermore, 90% of the hyperemia observed with IZBA® Solution were mild in severity[vi]. "Adverse effects such as redness of the eye or the discomfort related to hyperemia may reduce patient adherence to medication. Patients may perceive the treatment as unsuitable for them, even after the doctor has briefed them of expected side effects," said **Dato' Dr. Linda Teoh.**

Like TRAVATAN®[vii], IZBA® Solution is also formulated with POLYQUAD® preservative instead of benzalkonium chloride (BAK) which is more frequently associated with adverse reactions. Commonly found in contact lenses and artificial tears, POLYQUAD® helps reduce ocular surface issues. Adverse effects are the second most common reason behind patients switching medications after lack of efficacy[iv] . "Patient adherence may be affected due to intolerance to medication side effects which impact treatment outcomes and glaucoma progression. This increases the burden of monitoring and may require switching of treatment, thus increasing the cost of care," added **Dato' Dr Linda.**

"The goal of glaucoma treatment is to maintain visual function and preserve quality of life at a sustainable cost. As early glaucoma is often asymptomatic, prompt diagnosis and treatment before vision loss is important. Therapies which can improve adherence may contribute to slowing disease progression and preventing of blindness." concluded **Dr. Chang.**

(From left to right): **Patrick Grande**, Country President, Novartis Malaysia, Consultant Ophthalmologists and Glaucoma Specialists **Dr. Chang Yu-Fan**, Taipei Veterans General Hospital, **Dato' Dr. Linda Teoh**, Assunta Hospital, and **Dr. Mohd Aziz Husni**, Hospital Selayang, during the launch of IZBA®.

[i] IZBA Malaysia Prescribing Information, 75761-0; APPR 08 FEB 2018.
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[vii] Travatan Malaysia Prescribing Information. 759430; APPR 03 DEC 2018

Product Basic Succinct Statement is available on following page.
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Malaysian Journal of Ophthalmology

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Editorial

Smoke gets in your eyes

Shamira Perera[1,2,3,4]

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In this inaugural issue of Malaysian Journal of Ophthalmology, Nurul-Laila Salim and associates describe their case control study to determine the association between cigarette smoking and primary angle-closure glaucoma (PACG) in Malay patients. The authors should be commended on their efforts in investigating a regionally relevant and visually destructive disease and searching for presently elusive modifiable risk factors. Tight definitions of disease, a rigorous questionnaire process, and a well-delineated ethnic population are the strengths of this study, which continues the trend for high quality PACG research from the region.

Glaucoma includes a group of disorders characterized by progressive damage to the optic nerve associated with characteristic loss of the field of vision. It is the leading cause of irreversible vision impairment worldwide, with PACG a major subtype of glaucoma and cause of blindness, particularly in Asia. PACG is estimated to affect > 20 million people. The greatest challenge in preventing glaucoma blindness is identifying which individuals with PACG are at greatest risk of deterioration and development of advanced disease and what can be done to arrest disease progression. Unfortunately, the only well accepted modifiable risk factor at present is elevated intraocular pressure; this itself took many years to establish.

Although inconclusive, cigarette smoking has been thought to increase the risk of primary open-angle glaucoma (POAG), which is the more intensively studied type of glaucoma. However, the exact nature of this biologically plausible relationship is unclear, as the recent systematic review explains.[1] Some suggested that this association was related to the number of pack-years, as opposed to former smokers or passive smokers, but the dose-response effect is not clear. In contrast, PACG has been far less scrutinized and really only in-depth in regions where it is impossible to ignore, such as South East Asia. To see such a study on the Malaysian Malay population is a very much welcome development, as the results could be extrapolated to some extent to all Malays in the region, which number a sizeable population.

The type of investigation being used to its full effect here is a case control study, the stalwart of epidemiological studies to discover associations and their strength. The conclusions here pave the way toward more directed exploration to make the findings more meaningful, as again, there appears to be no logical dose-response relationship found, this time between smoking and PACG. Future cohort studies can examine causation and at what time point and intensity smoking can have its greatest impact so that fundamental research can be directed towards the mechanisms involved.

In Malaysia, smoking still has some social taboo attached, and yet its prevalence is surprisingly high and static (around 46% in males) despite sustained anti-smoking measures.[2] Some inroads have been made to decrease the prevalence of smoking, including curtailing advertising, designation of smoke-free areas, restructuring of tobacco taxes, anti-smoking campaigns, and the introduction of smoking cessation services at health clinics. This study adds to the weight of evidence behind the harms of smoking (beyond cancer and cardiovascular disease) and could be used to fuel further initiatives in public policy.

Based on the present study, ex-smoker and active smoker groups were not found to be significantly associated with PACG. However, there was a significant association between passive smokers and PACG in Malay patients residing in Malaysia. The importance of this novel finding resides in opening up the possibility to control the disease by modifying behaviors, which could be mediated via ramping up existing public health efforts against smoking in general.

Biometric and demographic risk factors for PACG have been well investigated and probably overshadow the effects of passive smoking in this population. Nevertheless, the increased risk of PACG to passive smokers is impressively large and an association such as this has not been seen in POAG to date. This novel finding is noteworthy, as many other studies have not considered the aspect of passive smoking, which might be the most amenable to intervention by carefully targeting families and workspaces with more information. The difficulty arises though, as the amount of passive smoking is difficult to quantify.

A separate, but related issue has grown since this study collected data: the controversial practice of vaping. A study from Klang in Malaysia[3] found that adult vapers perceived e-cigarettes as less toxic and healthier than cigarettes. However, whilst they are portrayed as less harmful and containing fewer contaminants, the chemicals contained in e-cigarettes are yet to be fully characterised and assessed for risk. Malaysia's 2019 ban on smoking at restaurants and eateries includes e-cigarettes if they contain nicotine, but how this will affect the passive smoking landscape remains to be seen.

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Original article

Anatomic predictors of intraocular pressure change after phacoemulsification: an AS-OCT study

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Abstract

Introduction: Phacoemulsification surgery is known to alter anterior segment structure parameters and also intraocular pressure (IOP). We set out in this study to investigate the relationship between the two parameters by using anterior segment optical coherence tomography (AS-OCT).
Purpose: To evaluate anterior segment and lens parameters associated with IOP lowering after phacoemulsification.
Study design: Prospective longitudinal single centre study.
Materials and methods: All consented study participants underwent uneventful phacoemulsification with foldable intraocular lens implantation. IOP measurement, gonioscopy, and AS-OCT measurements were performed pre- and postoperatively at one month. Customised software (Zhongshan Angle Assesment Programme, ZAAP) was used to measure various anterior chamber parameters. A-scan biometry

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was used to measure axial length (AL), lens thickness (LT), and to calculate lens position (LP) and relative lens position (RLP).
Results: Eighty-six eyes from 86 patients were included in this study. The mean IOP reduced significantly after phacoemulsification (from 16.2 ± 2.4 mmHg to 14.1 ± 2.6 mmHg at one week and 14.4 ± 2.3 mmHg at one month, $P < 0.001$). In the multivariate regression model, preoperative IOP and AL were the only significant parameters associated with percentage change in IOP ($p < 0.001$).
Conclusion: Change in IOP post-phacoemulsification is dependent on preoperative IOP and AL. Greater percentage change in IOP is seen in eyes with shorter axial length.

Keywords: angle-assessment programme, anterior segment optical coherence tomography (AS-OCT), axial length, intraocular pressure (IOP), phacoemulsification

Kajian AS-OCT: peramal anatomi ke atas perubahan tekanan intraokular selepas fakoemulsifikasi

Abstrak

Pengenalan: Pembedahan fakoemulsifikasi telah pun diketahui akan mengubah parameter struktur segmen anterior dan juga tekanan intraokular. Tujuan kami dalam kajian ini untuk menyiasat hubungan antara kedua-dua parameter dengan menggunakan segmen anterior OCT (ASOCT).
Tujuan: Untuk menilai parameter- parameter pada segmen anterior dan kanta yang dikaitkan dengan penurunan tekanan intraokular (IOP) selepas fakoemulsifikasi.
Reka bentuk kajian: Prospektif , pusat kajian tunggal.
Bahan dan kaedah: Persetujuan diambil daripada semua peserta kajian yang menjalani fakoemulsifikasi tanpa komplikasi dengan implantasi kanta intraokular fleksibel. Pengukuran IOP, pengukuran gonioskopi dan AS-OCT dilakukan sebelum pembedahan dan pascapembedahan bulan pertama (1). Perisian yang disesuaikan (Zhongshan Angle Assessment Program, ZAAP) digunakan untuk mengukur pelbagai parameter ruang anterior. Biometri A-scan digunakan untuk mengukur panjang paksi (AL), ketebalan lensa (LT), dan untuk mengira kedudukan lensa (LP) dan kedudukan kanta relatif (RLP).
Keputusan: Lapan puluh enam mata daripada 86 pesakit dimasukkan ke dalam kajian ini. IOP min berkurang dengan ketara selepas fakoemulsifikasi (dari 16.2 ± 2.4 mmhg kepada 14.1 ± 2.6 mmhg pada minggu 1 dan 14.4 ± 2.3 mmhg pada

bulan 1, P <0.001). Dalam model regresi multivariate, IOP pra-pembedahan dan panjang paksi adalah satu-satunya parameter penting yang dikaitkan dengan peratusan perubahan dalam IOP (p <0.001).
Kesimpulan: Perubahan dalam pascafakoemulsifikasi IOP bergantung kepada pra-pembedahan IOP dan panjang paksi. Peratusan perubahan yang lebih besar dalam IOP dilihat pada mata dengan panjang paksi yang lebih pendek.

Kata kunci: fakoemulsifikasi, segmen anterior OCT, tekanan intraokular, program penilaian sudut, panjang paksi

Introduction

The observation that intraocular pressure (IOP) often decreases after cataract surgery was first reported several decades ago.[1,2] These studies reported a variation of 1.4 mmHg to 13.5 mmHg in mean IOP reduction. The exact mechanism by which cataract operation reduces IOP remains unknown. Proposed mechanisms include relief of subclinical or intermittent angle narrowing, widening of the trabecular meshwork spaces and Schlemm's canal, and the effects of ultrasonic vibrations that occur during phacoemulsification on the trabecular meshwork cytokine release.[3-7]

Anterior segment structures can be objectively assessed using advanced imaging, such as Scheimpflug photography, ultrasound biomicroscopy, and anterior segment optical coherence tomography (AS-OCT). Numerous studies have focused on changes in angle configuration 1 to 12 months after cataract surgery using ultrasound biomicroscopy.[4,8,9] All studies report anterior chamber angle opening and anterior chamber deepening after cataract surgery.[4,10-15] Furthermore, it was reported that postoperative lowering of IOP was proportional to the increase in anterior chamber angle opening after phacoemulsification in eyes with narrow angles and open angles.[14,16,17] Huang *et al.* used AS-OCT to show that greater angle opening after cataract removal was significantly correlated with anterior chamber biometric factors, such as higher lens vault (LV), greater iris curvature (I-Curv), smaller trabecular-iris surface area (TISA), shallower anterior chamber depth (ACD), and narrower anterior chamber angle.[14] They also found that preoperative LV was a significant factor in IOP reduction. However, the association of other lens parameters, such as lens thickness (LT), lens position (LP), and relative lens position (RLP), as predictors of angle widening after cataract surgery were not investigated in their paper.

The purpose of this study was to determine the effects of phacoemulsification with intraocular lens (IOL) on IOP and anterior segment biometric parameters and, in particular, the association of lens biometric factors with anterior chamber angle widening and IOP reduction after surgery.

Methods

Data collection

This was a prospective, single centre study on patients undergoing phacoemulsification with IOL replacement at the University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. This study adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional review board approval was obtained from the Medical Ethics Committee of the University of Malaya Medical Centre prior to the start of the study. Written informed consent was obtained from all patients who agreed to participate in the study.

Inclusion criteria for patients included those scheduled to undergo routine phacoemulsification, at least 21 years of age, able to give informed consent, and possessing baseline IOP measurement of 21 mmHg or less on three different occasions preoperatively. The exclusion criteria included:

1. previous penetrating ocular surgery or refractive surgery;
2. primary or secondary glaucoma, peripheral and posterior anterior synechiae, glaucomatous optic neuropathy, or the use of topical glaucoma therapy;
3. substantial corneal abnormality, for example, corneal oedema, dystrophy, abrasion, marginal degeneration, and pterygium causing poor AS-OCT imaging quality;
4. vertical cup-to-disc ratio greater than 0.5, which may be consistent with glaucoma; and
5. complications related to the cataract surgery, for example, posterior capsule rupture and vitreous loss.

Pre- and postoperative evaluation

Preoperative evaluation included visual acuity testing, slit lamp examination, funduscopy, IOP measurement, gonioscopy, and biometry. Gonioscopy was performed using a Zeiss 4–mirror gonioscopy lens (Ocular Instruments, Bellavue, WA, USA) by a single glaucoma specialist (MZ) in a dark room setting. The Shaffer method of grading was used to grade all four quadrants. IOP was measured using Goldmann applanation tonometry by a single masked observer. Two readings were taken several minutes apart, and a separate observer read the measurement. If the two measurements differed by more than 2 mmHg, a third reading was taken and the average of three measurements was recorded. Patients were assessed within a narrow period of the day (9 am-1 pm) to reduce the effect of diurnal IOP fluctuation. Biometry was performed after slit lamp examination using an optical biometry device (Lenstar LS900, Haag-Streit AG, Bern, Switzerland). Axial length (AL) and lens thickness (LT) values were obtained from this device.

Following surgery, patients were reviewed in the eye clinic of UMMC at one week and one month postoperatively. All patients were given a postoperative regime of

tobramycin eye drops at two hourly intervals for the first week, which was tapered to four times daily for the following three weeks. At each visit, best-corrected visual acuity, slit lamp examination, IOP determination, and AS-OCT scan were performed by the same observer.

AS-OCT findings

Images of the anterior segment were collected by a single operator (LYC) two weeks before and one month after phacoemulsification cataract surgery using a commercially available AS-OCT device (Visante OCT; Carl Zeiss Meditec Inc., Dublin, California, USA). Standard resolution scans captured temporal and nasal quadrants in one image with the patient looking straight ahead. Only nasal and temporal quadrant images were included in this study, as assessment of the superior and inferior quadrants often requires manual manipulation of the eyelids, which may distort the angles. All the images were taken in the same dark conditions (0-1 lux ambient light by digital light meter [Easy View model EA30; Extech Instruments, Inc., Waltham, MA, USA]) with the patient sitting upright. Several scans were acquired by the operator, and only images with no motion artefacts or image artefacts resulting from the eyelids were chosen for analysis.

Images were analysed using the Zhongsan Angle Assesment Programme (ZAAP, Guangzhou, China), which has been shown to have good reproducibility for iris and corneal measurements by a single observer.[18,19] For each image, the only input by the observer was to determine the location of the two scleral spurs. The software then automatically calculates various parameters of the iris, cornea, and lens using automated identification of the anterior and posterior surfaces of the cornea, iris, and anterior surface of the lens. The images used for analysis were standard resolution images. Images were not used if scleral spurs were not located or a software delineation error occurred.

Anterior chamber parameters, such as anterior chamber depth (ACD), anterior chamber width (ACW), anterior chamber area (ACA), anterior chamber volume (ACV), angle opening distance (AOD) at 500 microns and 750 microns, and lens vault (LV) based on AS-OCT imaging, were compared preoperatively and one week and one month postoperatively.

Anterior vault (AV) was calculated as ACD+LV and relative LV (RLV) was calculated by dividing the LV by AV. The intra-observer reproducibility of the iris measurements was assessed using a random subset of 20 preoperative images. A single observer (LYC) analysed the images twice on occasions separated by an interval of at least one month.

Surgical technique

A consultant ophthalmologist (NR) performed all the cataract removals using conventional phacoemulsification. After a 2.75 mm clear corneal tunnel incision, a continuous curvilinear capsulorrhexis measuring approximately 5 to 6 mm in

diameter was created using a cystotome and Utrata forceps. Hydrodissection/hydrodelineation, phacoemulsification, cortical aspiration, insertion of a foldable acrylic IOL in the capsular bag and intracameral carbachol instillation at the end of surgery were then performed step by step. All the participating patients received a single-piece acrylic IOL in their eyes.

Statistical analysis

Statistical analysis was performed using the statistical package IBM SPSS Statistics for Windows (Version 21.0; IBM Corp., Armonk, NY, USA). Paired t-test was used to assess the one-month postoperative changes in the continuous variables. Univariate linear regression analyses adjusted for age and sex were performed for baseline parameters with percentage change in mean IOP (calculated as follows: difference in IOP at one month and preoperative IOP/preoperative IOP multiplied by 100) as the dependent variable. This was followed by a multivariate linear regression analysis using baseline parameters that showed significance at 0.20 levels in univariate analysis, excluding those that showed multicollinearity. Variance inflation factor and tolerance were calculated to test potential multicollinearity among the independent variables. The R2 was evaluated to examine the adequacy of the multiple linear regression models. Intra-observer agreement and inter-mode (standard and enhanced resolution images) agreement were performed to assess the repeatability of AS-OCT images. Probability values less than 0.05 were considered statistically significant.

Results

A total of 108 eyes from 108 patients had uneventful phacoemulsification and agreed to participate in the study during the specified time period. Among them, 22 patients were excluded from the study, as 18 had software delineation errors and 6 had poor visualisation of the scleral spurs on AS-OCT images. With the exclusions, 86 eyes (79.63%) were eligible for the final analysis. Twelve eyes (13.95%) had Schaffer grades of 2 or less in ≥ 2 quadrants by gonioscopy, and 74 (86.05%) eyes had Schaffer grades of 3 or 4 in ≥ 2 quadrants. Table 1 provides the patient demographics and baseline clinical data.

Table 2 lists the pre- and posoperative measurements of IOP, AOD500, ACD, ACA, ACW, ACV, and central corneal thickness (CCT) by one-way analysis-of-variance (ANOVA) models and multiple-comparison tests. Significant increases in the angle and anterior segment parameters were observed at one month after phacoemulsification with IOL implantation. Significant changes were present in terms of IOP and angle parameters.

Table 3 shows the age and sex adjusted univariate regression model, indicating the association between percentage reduction in IOP after phacoemulsification and

Table 1. Baseline demographics and ocular parameters of patients

N = 86	Mean ± SD	Range
Age (years)	63.70 ± 8.75	30-78
IOP (mmHg)	16.24 ± 2.46	10-22
AOD750 (mm)	0.652 ± 0.288	0.15-1.71
TISA750 (mm)	0.368 ± 0.18	0.05-1.05
IT750 (mm)	0.461 ± 0.07	0.33-0.68
Iarea (mm^2)	1.683 ± 0 .23	1.26-2.72
Icurv (mm)	0.280 ± 0.13	0.04-0.69
Ivolume (mm^3)	16.486 ± 2.20	11.98-22.45
ACD (mm)	2.892 ± 0.39	2.12-3.99
ACW (mm)	11.40 ± 0.37	10.44-12.19
ACA (mm^2)	21.87 ± 3.76	15.59-33.63
ACV (mm^3)	91.01 ± 19.13	58.92-148.58
Pupil diameter (mm)	3.63 ± 0.85	1.72-5.81
AV (mm)	3.049 ± 0.19	2.48-3.57
RLV (mm)	0.051 ± 0.12	-0.22-0.29
AL (mm)	23.860 ± 1.26	21.8-27.8
LT (mm)	4.437 ± 0.70	2.41-5.90
LP (mm)	5.044 ± 0.34	3.60-5.98
RLP (mm)	0.211 ± 0.02	0.164-0.260

Intraocular pressure: IOP; angle opening distance at 750 microns from scleral spur: AOD 750; trabecular-iris surface area: TISA; iris thickness: IT; iris area; Iarea; iris curvature: Icurv; iris volume Ivolume; anterior chamber depth: ACD; anterior chamber width: ACW; anterior chamber area: ACA; anterior chamber volume: ACV; lens vault: LV; anterior vault: AV, calculated as ACD+LV; relative lens vault: RLV, calculated by dividing the LV by AV; axial length: AL; lens thickness: LT; lens position: LP; relative lens position: RLP

Table 2. Changes in mean anterior segment parameters following cataract extraction

	Preop	1 month postop	Mean difference (95%CI)	P-value
IOP (mmHg)	16.24 ± 2.46	14.47 ± 2.39	1.77 (1.22,2.31)	< 0.001
AOD750	0.64 ± 0.29	1.02 ± 0.21	-0.38 (-0.46, -0.29)	< 0.001
TISA750	0.36 ± 0.18	0.55 ± 0.13	-0.19 (-0.24, -0.15)	< 0.001
IT750	0.46 ± 0.07	0.44 ± 0.08	-0.19 (-0.24, -0.14)	0.19
Iarea	1.65 ± 0.24	1.64 ± 0.21	0.01 (-0.07, 0.09)	0.88
Icurv	0.29 ± 0.13	0.18 ± 0.08	0.11 (0.07, 0.14)	< 0.001
Ivolume	16.54 ± 2.26	15.94 ± 2.04	0.59 (-0.21, 1.39)	0.15
ACD (mm)	2.89 ± 0.3	4.11 ± 0.30	-1.24 (-1.35, -1.13)	< 0.001
ACW (mm)	11.40 ± 0.37	11.35 ± 0.36	0.04 (-0.65, 0.15)	0.44
ACA (mm^2)	21.87 ± 3.76	28.77 ± 2.64	-7.17 (-8.19, -6.17)	< 0.001
ACV (mm^3)	91.01 ± 19.13	115.88 ± 13.62	-26.11 (-31.32, -20.91)	< 0.001
Pupil diameter	3.65 ± 0.86	3.45 ± 0.72	0.19 (-0.04, 0.43)	0.11

Analysis done with paired t-test. Intraocular pressure: IOP; angle opening distance at 750 microns from scleral spur: AOD750; trabecular-iris surface area: TISA; iris thickness: IT; iris area: Iarea; iris curvature: Icurv; iris volume: Ivolume; anterior chamber depth: ACD; anterior chamber width: ACW; anterior chamber area: ACA; anterior chamber volume: ACV

Table 3. Linear regression analysis of the determinants for postoperative percentage IOP change

	Univariate regression analysis			Multivariate regression analysis		
	B(SE)	**Beta**	**P-value**	**B(SE)**	**Beta**	**P-value**
Age	-0.13 (0.213)	-0.68	0.53	-0.112 (0.218)	-0.057	0.61
Gender	-0.53 (3.72)	0.016	0.89	2.998 (3.40)	0.088	0.38
IOP	3.71 (0.68)	0.538	< 0.001*	3.387 (0.69)	0.491	< 0.001*
AOD750	9.56 (6.55)	0.162	0.15			
TISA750	15.49 (10.76)	0.161	0.15	7.815 (17.09)	0.081	0.65
IT750	22.98 (29.07)	0.093	0.42			
Iarea	0.09 (8.644)	0.001	0.99			
Icurv	-17.24 (14.54)	-0.134	0.24			
Ivolume	0.20 (0.90)	0.026	0.82			
ACD (mm)	6.36 (4.80)	0.145	0.19			
ACW (mm)	-5.40 (5.15)	-0.116	0.29			
ACA (mm^2)	0.64 (0.50)	0.143	0.19			
ACV (mm^3)	0.108 (0.099)	0.122	0.27			
LV	-9.12 (5.27)	-0.19	0.09*	-0.409 (8.55)	-0.008	0.96
AV	-4.34 (9.682)	-0.049	0.66			
RLV	-26.70 (16.05)	-0.182	0.10			
AL	-3.69 (1.45)	-0.274	0.01*	-3.028 (1.26)	-0.225	0.018*
LT	5.19 (3.04)	0.215	0.09*	3.417 (2.62)	0.141	0.19
LP	-3.03 (5.43)	-0.062	0.56			
RLP	136.17 (116.96)	0.127	0.25			
CCT	-0.001 (0.04)	-0.001	0.99			

Intraocular pressure: IOP; angle opening distance at 750 microns from scleral spur: AOD750; trabecular-iris surface area: TISA; iris thickness: IT; iris area: Iarea; iris curvature: Icurv; iris volume Ivolume; anterior chamber depth: ACD; anterior chamber width: ACW; anterior chamber area: ACA; anterior chamber volume: ACV; lens vault: LV; anterior vault: AV, calculated as ACD+LV; relative lens vault: RLV, calculated by dividing the LV by AV; axial length: AL; lens thickness: LT; lens position: LP; relative lens position: RLP; central corneal thickness: CCT

various preoperative ocular parameters. Preoperative parameters such as IOP, TISA 750, LV, AL, and LT were considered significant at $p < 0.20$ value. Further multivariate regression analysis of these five parameters showed that only preoperative IOP and AL remained statistically significant.

Discussion

This study showed significant reduction of IOP at one week and one month after phacoemulsification, with mean IOP reduction of 1.77 mmHg at one month postoperatively. The present findings were similar to previous studies conducted in non-glaucomatous patients, which showed a reduction in IOP between 1.26 mmHg and 2.82 mmHg.[13,14,20] This study suggests that after adjusting for age and sex, preoperative IOP and AL are independent predictors of reduction in IOP after surgery.

Prediction of IOP reduction post-phacoemulsification has been the subject of various studies.[13,14,16,17] Some have come up with novel indexes, such as preoperative IOP to preoperative ACD ratio.[16] Yet others have associated preoperative anatomic parameters measured by biometry, UBM, or AS-OCT with postoperative IOP reduction.[12,14,21]

We did not find any lens parameters (LV, LT, LP, RLP) that predicted the postoperative reduction in IOP. This differs from the findings of Huang *et al.*, which showed LV to be significantly correlated with IOP reduction after cataract surgery.[14] This disparity may be due to a difference in study patients. In the study by Huang *et al.*, there was a higher percentage of angle closure eyes (39.73%) compared to ours (13.95%), which corresponds to their higher LV mean of 580 µm when compared to 157 µm in our study.

Yang *et al.* also found LT, ACA, and AOD500 to be significant factors in predicting IOP change after phacoemulsification.[20] Two other studies showed that IOP reduction in angle closure was significantly greater than in open angle eyes.[4,13] Due to the limited number of angle closure patients in our cohort, we were unable to make any meaningful comparisons between this group and the open angle patients. We did however find that AL measurements were inversely proportional to percentage IOP change. This seems to support the findings that shorter eyes, which are more likely to be hypermetropic, show significant IOP change post-phacoemulsification. Yet another study found that, along with high iris cross-sectional area and convex hull of the iris, preoperative IOP was a good predictor of long-term IOP reduction post-phacoemulsification.[21] Our study did not find these parameters significant.

We suspect that small differences in outcome are related to the differences in assessing the anterior chamber and lens parameters. Similar to our study, Huang *et al.* utilised the ZAAP software for image processing and subsequent calculations.[13,14] Others have used customised software (ImageJ software; National Institutes of Health, Bethesda, Maryland, USA)[20] or have calculated parameters using simple

measurement software available on the AS-OCT machine itself.[11,21,22] Differences in measurement methods, whether by manual or by customised software on the AS-OCT may account for the discrepancy in study findings. This issue has also been seen in previous studies using UBM or gonioscopic assessment that were open to subjective errors in assessment and marking of anatomical landmarks.[8,10,12,16]

There were several limitations to our study. The number of participants having angle closure eyes was very small. As such, we were unable to assess if there were differences between angle closure and open angle eyes. Additionally, the follow-up of one month was relatively short in duration. As corneal biomechanical properties (including corneal rigidity) change in the early postoperative period, this may affect the IOP measurement. Corneal biomechanical parameters will reach preoperative values by three months after phacoemulsification.[23] Therefore, a longer follow-up of at least three months would have been more accurate in evaluating the long-term association between IOP reduction and anterior chamber and lens parameters after phacoemulsification.

Conclusion

In conclusion, this study has shown that IOP reduction post-phacoemulsification is predicted by preoperative IOP and AL. Eyes with shorter AL demonstrate greater postoperative IOP reduction. Angle and lens parameters measured with AS-OCT did not predict percentage of IOP reduction in patients undergoing routine phacoemulsification surgery.

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Original article

Malay Glaucoma Eye Study (MaGES): cigarette smoking and primary angle-closure glaucoma

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Abstract

Introduction: The detrimental effects of cigarette smoking include impairment of optic nerve head perfusion and elevation of oxidative stress levels, which are believed to be part of the pathogenesis of glaucoma. However, there is no evidence on the effect of cigarette smoking as a risk for primary angle-closure glaucoma (PACG).

Purpose: To determine the association between cigarette smoking and PACG in Malay patients.

Study design: Case control study.

Materials and methods: Two-hundred Malay PACG patients and 250 controls from

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three tertiary hospitals in Malaysia were involved in this study. PACG patients were diagnosed based on the World Glaucoma Association consensus. The smoking status was documented using validated questionnaire adopted from Singapore Malays Eye Study through face-to-face interview. Smoking status was divided into active smokers, ex-smokers, passive smokers, and non-smokers. The association of smoking and PACG was analysed with multiple logistic regression. Confounders such as age, gender, education status, and body mass index (BMI) were considered in the analysis.

Results: There was female preponderance in PACG with 3:1 ratio. Active smokers ($p = 0.656$) and ex-smokers (0.073) were not significantly associated with PACG in Malays. Passive smoking significantly increased the risk of PACG by 6.8-fold (95% CI 2.49,18.67; $p < 0.001$). Number of cigarettes/day ($p = 0.144$) and duration of smoking ($p = 0.176$) were also not significantly associated with PACG ($p = 0.144$). No formal education, primary and secondary education level increased the risk of PACG ($p < 0.001$). Each unit increment of BMI increased the risk of PACG by 1.14-fold (95% CI 1.03, 1.27; $p = 0.014$). A year increased in age increased the risk by 1.05 times (95% CI 1.00, 1.09; $p = 0.026$).

Conclusions: There is no significant association between active smoking and PACG. Passive smoking is a potential risk factor for PACG. The preponderance of women may contribute to this result. However, quantification of exposure to passive smoking is not possible in this study.

Keywords: cigarette smoking, Malay, passive smokers, primary angle-closure glaucoma (PAGC), risk factors

Kajian Mata Glaukoma Bangsa Melayu (MaGES): merokok dan glaukoma sudut tertutup primer

Abstrak

Pengenalan: Kesan kemudaratan disebabkan oleh rokok termasuklah gangguan perfusi kepala saraf optik dan peningkatan tahap tekanan oksidatif, yang dipercayai menjadi sebahagian daripada patogenesis glaukoma. Walau bagaimanapun, tidak ada bukti mengenai kesan rokok sebagai risiko untuk glaukoma sudut tertutup primer (PACG).

Tujuan: Untuk menentukan perkaitan antara merokok dan PACG dalam kalangan pesakit Melayu.

Reka bentuk kajian: Kajian kawalan kes.

Bahan dan kaedah: Dua ratus pesakit PACG dari bangsa Melayu dan 250 kawalan

dari tiga hospital tertier di Malaysia terlibat dalam kajian ini. Pesakit PACG didiagnos berdasarkan persetujuan am Persatuan Glaukoma Dunia. Status merokok didokumenkan menggunakan soal selidik yang telah disahkan yang diambil daripada Kajian Melayu Mata Singapura Singapura melalui temu ramah secara bersemuka. Status perokok dibahagikan kepada perokok aktif, bekas perokok, perokok pasif, dan bukan perokok. Perkaitan antara merokok dan PACG dianalisis dengan menggunakan kaedah regresi logistik berganda. Konflik dalaman seperti umur, jantina, status pendidikan, dan indeks jisim badan (BMI) dipertimbangkan dalam analisis.

Keputusan: Terdapat lebih ramai wanita didapati mengalami PACG dengan nisbah 3: 1. Perokok aktif (p = 0.656) dan bekas perokok (0.073) didapati tidak berkait secara ketara dengan PACG bangsa Melayu. Perokok pasif secara signifikan meningkatkan risiko PACG sebanyak 6.8 kali ganda (95% CI 2.49,18.67; p <0.001). Bilangan rokok / hari (p = 0.144) dan tempoh merokok (p = 0.176) juga tidak dikaitkan dengan PACG (p = 0.144). Tiada pendidikan formal, tahap pendidikan rendah dan menengah meningkatkan risiko PACG (p <0.001). Setiap peningkatan unit BMI meningkatkan risiko PACG sebanyak 1.14 kali ganda (95% CI 1.03, 1.27; p = 0.014). Satu tahun peningkatan umur meningkat risiko sebanyak 1.05 kali (95% CI 1.00, 1.09; p = 0.026).

Kesimpulan: Tidak terdapat hubungan yang signifikan antara aktiviti merokok aktif dan PACG. Aktiviti merokok pasif adalah faktor risiko yang berpotensi untuk PACG. Jumlah wanita yang lebih ramai dalam kajian ini mungkin menyumbang kepada hasil kajian ini. Walau bagaimanapun, pengiraan kuantifi pendedahan kepada merokok pasif tidak dilakukan dalam kajian ini.

Kata kunci: merokok, Melayu, perokok pasif, glaukoma sudut tertutup primer (PAGC), faktor risiko

Introduction

Primary angle-closure glaucoma (PACG) is believed to cause more blindness in the Asian population than in other populations.[1] Asians constitute an heterogenous, multi-ethnic population. There are many studies on this irreversible disease among the Chinese,[2-4] Japanese,[5,6] and Indian[7-9] populations. However, there is limited knowledge of PACG in the Malay population. Based on the Singapore Malay Eye Study (SiMES), 150 (4.6%) of 3280 participants were diagnosed with glaucoma. After age and sex standardization, the prevalence of primary open-angle glaucoma (POAG) was 2.5%, PACG was 0.12%, and secondary glaucoma was 0.61% among Malays residing in Singapore.[10]

Angle closure is not uncommon in Malays.[11] A retrospective hospital-based study in two different hospitals found that Malay patients presented at more advanced

stage and progressed faster compared to Chinese patients in Malaysia.[12] However, the outcome of this study is affected by potential biases from the nature of the study and differences in the management between the two centres.[12] Understanding the clinical presentation of PACG in Malays is important to formulate a blindness prevention strategy in the Asian population.

Several risk factors for PACG have been identified. Older age, family history, female, and Chinese ethnicity are among the important non-modifiable risk factors for PACG.[13-15] Shorter axial length, shallow anterior chamber depth, increased iris thickness and anteriorly positioned lens are the ocular biometry parameters associated with PACG.[16-18] The identification of modifiable risk factors is crucial in preventive measures of blindness in glaucoma. At present, the only modifiable risk factor for glaucoma is intraocular pressure (IOP).[19,20]

Although inconclusive, cigarette smoking is found to increase the risk of POAG.[21,22] Noxious substances in cigarettes may cause elevation of oxidative stress markers[23,24] and changes in vascular integrity in the optic nerve head,[25,26] which have been postulated as part of POAG pathogenesis. Cigarette smoking may also exert similar detrimental effects in PACG patients. To the best of our knowledge, there is no study looking into cigarette smoking as a potential risk factor for PACG. The aim of this study was to evaluate the potential effects of cigarette smoking as a modifiable risk factor for PACG.

Materials and methods

A case control study was conducted between April 2014 and May 2016 involving patients attending ophthalmology clinics of tertiary centres in Kelantan state: Hospital Universiti Sains Malaysia (HUSM) and Hospital Raja Perempuan Zainab II (HRPZII); and Kedah state: Hospital Sultanah Bahiyah (HSB). Malaysia is a multi-ethnic country, with Malays representing 50.1% of the population, Chinese 22.6%, indigenous people 11.8%, and Indians 6.7%.[27] Kelantan and Kedah are among the states with a majority of Malay population.[27]

This study received ethical approval from the research and ethics committee of the School of Medical Sciences, Universiti Sains Malaysia and from National Medical Research and Ethics Committee, Ministry of Health Malaysia. This study was conducted in accordance to the Declaration of Helsinki for human research.

This study is part of the Malay Glaucoma Eye Study (MaGES). MaGES is a multicentre study with the aim of identifying modifiable risk factors for glaucoma development and progression in Malays residing in Malaysia. A total of 200 PACG patients (90 from HUSM, 90 from HRPZII, and 20 from HSB) and 250 control subjects were recruited. Malay was defined based on three generations of Malay lineage. Pedigree charts were drawn to exclude potential inter-racial marriages or incomplete pedigree charts. PACG was based on the World Glaucoma Association

consensus definition.[28] Primary angle-closure suspect (PACS), primary angle-closure (PAC), and glaucoma suspect patients were excluded from the study. Patients with conditions that may affect the visual field, such as retinal diseases and neurological diseases, were excluded. Those with a history of cerebrovascular accidents and memory problems including dementia were also excluded.

Control subjects were recruited from the HUSM, HRPZII, and HSB ophthalmology clinics. They were selected based on simple random sampling among non-glaucoma patients who presented with dry eye, pterygium, and other ocular problems. A thorough ocular examination was conducted including slit lamp examination and fundus examination to rule out glaucoma. Gonioscopic examination was also conducted to rule out angle closure. Goldman applanation tonometry (Haag-Streit, Switzerland) was used to measure IOP. Those with IOP more than 20 mmHg were excluded. Humphrey visual field (HVF) 24-2 analysis was also conducted to rule out potential glaucomatous changes. Subjects who had a family history of glaucoma, history of cerebrovascular accident, and memory problems as well as glaucoma suspects were also excluded.

Weight and height of the recruited PACG patients and control subjects were obtained and body mass index (BMI) was calculated. Data on cigarette smoking was obtained using a validated questionnaire from Singapore Malay Eye Studies (SiMES) and conducted via face-to-face interview by two investigators (NLS and PS). NLS was responsible for recruitment in Kelantan state and PS was responsible for recruitment in Kedah state. The following were based on World Health Organization definitions:[29]

1. Active smoker: someone who, at the time of survey, smokes any tobacco product either daily or occasionally.
2. Ex-smoker: individual who was formerly a daily smoker, but currently does not smoke at all.
3. Passive smoker: individual who inhales cigarette smoke from the surrounding environment without directly smoking a cigarette, including smoke exhaled by active smokers (second-hand smoke); burning off the tip of the cigarette (side stream smoke); and seeping through the paper and filter of a lit cigarette (lateral stream smoke).

Subjects were required to recall cigarette smoking exposure since childhood for as long as they could remember. Pipe smoking, cigar, and rollups were converted to cigarette smoking equivalence.

Statistical analysis was performed using Statistical Analysis Software Package (SPSS) software, version 22. Simple logistic regression analysis was done for univariate analysis on predictors for PACG. Subsequently, multivariate analysis was done using multiple logistic regression method. The parameters were checked for possible interactions using enter method. A P-value of less than 0.05 was considered statistically significant.

Table 1. Demographic characteristics between PACG patients and control subjects

Variables	PACG (n = 200)	Control (n = 250)	p-value
Age (mean ± SD)	66.4 ± 8.80	60.9 ± 9.99	< 0.001
Gender (n, %)			< 0.001
Male	50 (25%)	145 (58.0%)	
Female	150 (75%)	105 (42.0%)	
Education level (n, %)			< 0.001
No formal education	29 (14.5%)	4 (1.6%)	
Primary level	89 (44.5%)	65 (26.0%)	
Secondary level	70 (35.0%)	100 (40.0%)	
Tertiary level	12 (6.0%)	81 (32.4%)	
BMI (mean ± SD)	24.99 ± 3.85	23.98 ± 1.67	< 0.001

#Pearson Chi-square test ($p < 0.05$ is significant)

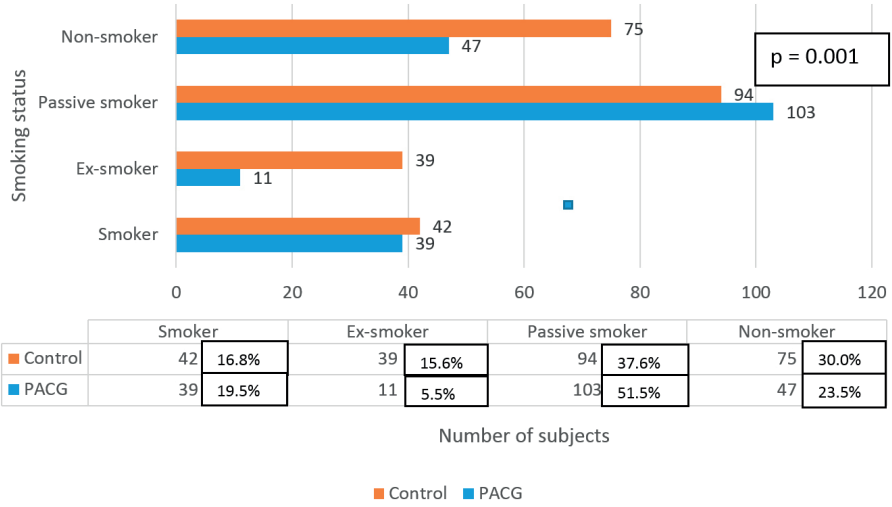

Fig. 1. Distribution of PACG patients and control subjects according to smoking status. Pearson Chi-square test ($p < 0.05$ is significant).

Results

A total of 450 Malay subjects (200 PACG patients and 250 control subjects) were enrolled in this study. PACG patients were significantly older compared to control

Table 2. Smoking quantity of smokers and ex-smokers among PACG and control subjects

Variable	Status		p-value
	PACG (n = 50)	Control (n = 81)	
Smoking exposure			0.176^
Duration,mean years ± SD	33.54 (15.38)	36.68 (10.97)	
Number of cigarettes per day			0.144#
1 to 10 sticks	32 (64%)	38 (46.9%)	
11 to 20 sticks	16 (32%)	40 (49.4%)	
More than 20 sticks	2 (4%)	3 (3.7%)	

^Independent t-test ($p < 0.05$ is significant); #Pearson Chi-square test ($p < 0.05$ is significant)

subjects. There was significant difference in sex distribution between PACG patients and controls (Table 1), with female preponderance among PACG patients (75%). The majority of patients received at least primary education (85.5%), while 29 (14.5%) PACG patients had no formal education. PACG patients have significantly higher mean BMI compared to controls (Table 1).

A total of 103 (51.5%) PACG patients were passive smokers. Only 39 (19.5%) PACG patients were active smokers (Fig. 1). A total of 150 (75%) PACG patients were passive or non-smokers, while 169 (67.6%) were passive or non-smokers among the control subjects (Fig. 1). There was no significant difference in duration of smoking among smokers and ex-smokers between PACG and control subjects (Table 2). There was also no significant difference in the number of cigarettes smoked per day between PACG and control subjects ($p = 0.144$) (Table 2). Only 13 out of 255 female respondents were smokers or ex-smokers; all of them were PACG patients.

Based on multivariate analysis, passive smoking is significantly associated with PACG ($p < 0.001$) (Table 3). Passive smoking increased the risk of PACG by 6.8-fold (95% CI 2.49, 18.67). In this study, there was no significant association between ex-smokers and active smokers to PACG (Table 3). Lower education status increased the risk of PACG; no formal education significantly increased the risk for PACG by 48.9-fold (95% CI 14.62, 168.86; $p < 0.001$) and primary level of education increased the risk for PACG by 18.3-fold (95% CI 4.53, 73.95; $p < 0.001$). Females were at higher risk for PACG [5.3 fold (95% CI 2.37, 11.50; $p < 0.001$)]. BMI is also a significant associated factor for PACG. With each 1 unit increment of BMI, there is 1.14 times higher chance to have PACG (Table 3).

Table 3. Logistic regression analysis of associated factors for PACG

Variable	Simple logistic regression				Multiple logistic regression			
	b	OR[c] (95% CI)	Wald statistics	p-value*	b	OR[a] (95% CI)	Wald statistics	p-value*
Smoking status								
Passive smoker	0.39	1.48 (0.84, 2.62)	1.84	0.175	1.92	6.82 (2.49, 18.67)	13.96	< 0.001
Ex- smoker	-0.80	0.45 (0.21, 0.96)	4.22	0.040	-0.20	0.82 (0.27,2.51)	0.12	0.730
Active smoker	0.56	1.75 (1.10, 2.77)	5.68	0.017	0.15	1.16 (0.60, 2.23)	0.19	0.666
No. of cigarettes per day								
11 to 20 sticks	-0.74	0.48 (0.23, 1.00)	3.82	0.475	0.01	1.01 (0.33, 3.04)	0.00	0.992
More than 20	-0.23	0.79 (0.12, 5.04)	0.06	0.805	1.53	4.59 (0.55, 38.37)	1.98	0.159
Duration of smoking (years)	-0.02	0.99 (0.96, 1.01)	1.99	0.158	-0.05	0.95 (0.90, 1.01)	2.90	0.089
Age	0.06	1.06 (1.04, 1.08)	32.05	< 0.001	0.04	1.04 (0.10, 1.08)	3.40	0.065
Gender								
Female	1.42	4.14 (2.76, 6.22)	46.89	< 0.001	1.66	5.25 (2.37, 11.60)	16.76	< 0.001
BMI	0.13	1.14 (1.06, 1.22)	12.80	< 0.001	0.13	1.14 (1.02, 1.27)	5.76	< 0.001
Education								
Secondary level	1.55	4.73 (2.40, 9.32)	20.10	< 0.001	2.24	9.40 (2.67, 33.04)	12.20	< 0.001
Primary level	2.22	9.24 (4.66, 18.34)	40.44	< 0.001	2.91	18.31 (4.53, 73.95)	16.66	< 0.001
No formal education	3.89	48.94 (14.62, 163.86)	39.82	< 0.001	3.87	48.04 (8.3, 277.99)	18.69	< 0.001

*Multiple logistic regression ($p < 0.05$ is significant); b: regression coefficient; OR[c]: crude odd ratio; OR[a]: adjusted odd ratio

Discussion

The quest for potential modifiable risk factors for glaucoma has been a daunting task. Until now, IOP remains the only modifiable risk factor for glaucoma. Cigarette smoking has been implicated as a risk factor for ocular diseases such as age-related macular degeneration[30,31] and retinal vein occlusion.[32] It is also a known risk factor for stroke,[33] cardiovascular diseases,[34,35] and peripheral vascular diseases.[36]

Based on the present study, the ex-smoker and active smoker groups were not found to be significantly associated with PACG. There was a significant association between passive smokers and PACG. Passive smoking increased the risk of PACG by 6.8-fold (95% CI 2.49, 18.67). Higher number of passive smokers was found among PACG patients compared to controls. This is perhaps due to the sex preponderance, as women are more at risk of developing PACG.[1,37] Similarly, women were at higher risk of developing glaucoma in the present study. This is perhaps related to their ocular biometry: women tend to have a shorter axial length and shallower anterior chamber, leading to crowding of the angle and impaired aqueous outflow.[37-40] Ocular biometrical factors and crowding of the angle are established risk factors for PACG.[16-18]

In general, cigarette smoking is more prevalent among men, although currently, the prevalence among younger women is increasing.[41] Among the elderly population, only 2.9% of Malaysian women are active smokers and 3.4% are ex-smokers, in contrast to 28.1% of active smokers and 23.2% ex-smokers among men.[42] Across all ages, the prevalence of Malaysian women who smoke is about 1.7% of the Malaysian population.[43] Although there is no precise estimate of Malay smokers according to sex distribution, the prevalence of Malay smokers is 2.5 times higher compared to the Chinese population in Malaysia.[44] With higher prevalence of PACG among women, a higher percentage of passive smokers among PACG is expected.

It is believed that the detrimental effects of cigarette smoking to passive smokers are similar than those to active smokers. Numerous studies have shown that passive smoking may cause detrimental effects to vascular integrity and elevation of oxidative biomarkers similar to active smoking.[45-48] Cigarette smoking is postulated to cause impaired ocular perfusion,[49,50] increased oxidative stress markers,[23,24] and IOP elevation.[51] There is conflicting evidence on the role of cigarette smoking in POAG.[21,22,52,53] However, no studied found an association between passive smoking and POAG.

Cigarette smoking is also affected by socioeconomic status and education level.[54,55] Higher prevalence of smokers is seen among those with lower socioeconomic and educational levels in various countries.[55] PACG prevalence is higher among those living in socioeconomic deprivation.[56,57] However, we did not include household income to determine socioeconomic status in this study. A lower education level is exponentially related to lower socioeconomic status.[58] Elderly women in our present study were mainly unemployed and had lower educational

level. There was a significant association between education level and risk of PACG in the current study. A lower education level is usually associated with financial difficulties that may deter health-seeking behaviour.[59] In addition, lower education level may also cause poor awareness in asymptomatic diseases such as glaucoma, even among those with APAC.[60,61]

In the present study, the exact number of household members that smoke cigarettes at a certain point of time was not documented. Thus, the exact amount of exposure to the noxious substances from cigarette smoking (as passive smokers) cannot be quantified. Smoking among women is a social taboo and stigmatised as morally flawed in Malay culture.[62] This was reflected in the small number of women who smoked, both among PACG patients and controls. Due to this, there is also a probability that some of the subjects may not admit to smoking due to this perceived social taboo in Malay culture.

There has been limited research on the association between cigarette smoking and PACG. Based on the medical database of one hospital in China involving 662 PACG patients, the odds ratio of cigarette smoking was 0.515 (95% CI 0.293.0.906, $p < 0.05$).[63] Previous studies were mainly focused on the association between smoking and POAG.[64-66] Current studies on the effect of smoking on POAG showed inconclusive and often contradictory findings. This is probably due to the complex interaction of multiple factors, such as environmental exposure, that may be modified by genetic factors.[66]

Using questionnaires to assess cigarette smoking requires subjects to recall their cigarette smoking exposure for as long as they can remember. Although only subjects who were able to recall their cigarette smoking exposure were recruited for this study, recall bias was inevitable in view of the long recall duration required. Due to study design, the point in time at which cigarette smoking behaviour affected the optic nerve head causing glaucomatous changes could not be determined. A prospective cohort study design would be a better option to ensure that the exact quantity of cigarette and exact time point of insult can be assessed.

Conclusion

Passive smoking is found to be significantly associated with PACG in Malay patients residing in Malaysia. Although active and ex-smokers were not found to be significantly associated with PACG in this study, smoking cessation is advised owing to the clear evidence of damage related to other ocular and systemic diseases, as well as its potential harmful effect to vascular integrity.

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Original article

Intraocular silicone oil removal: timing, outcome, and silicone oil complications encountered

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Abstract

Introduction: Silicone oil is the preferred tamponade agent used in pars-plana vitrectomy for retinal detachment when a long duration of endotamponade is intended. Due to its possible long-term complications, removal of silicone oil (ROO) is recommended.
Purpose: This study is done to evaluate the mean duration and complications of silicone oil tamponade, and the anatomical and visual outcomes after silicone oil removal.
Study design: Retrospective study.
Materials and methods: Retrospective review was done on 55 eyes of 55 patients, in which ROO was carried out at Hospital Sultanah Bahiyah in 2016 with a minimum six months follow-up postoperatively.
Results: The duration of silicone oil tamponade in these eyes ranged from 1.0 to 55.5 months, with mean duration of 10.8 months (SD 7.74). Common complications of silicone oil tamponade observed were cataract in 30 eyes (54.5%), followed by secondary high intraocular pressure in 6 eyes (10.9%), and band keratopathy in 3 eyes (5.5%). Six eyes (10.9%) developed retinal re-detachment after oil removal.

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The majority in the anatomically attached group post ROO (40 eyes, 81.6%) showed improvement of vision after ROO, with mean best corrected vision of LogMAR 1.38 (6/150) with silicone oil in situ to LogMAR 0.88 (6/48) at the latest follow-up.
Conclusions: Although the recommended duration of silicone oil tamponade ranges from three to six months, the optimal timing for silicone oil removal still remains unknown. ROO is recommended due to oil-related complications, but the anatomical outcome should be evaluated as well. However, in our setting, with limited resources and time, and increasing number of patients indicated for silicone oil, it is impossible to comply with the recommended time for ROO and the timing is usually set on an individual basis.

Keywords: cataract, glaucoma, internal tamponade, keratopathy, pars-plana vitrectomy, retinal detachment, silicone oil

Penyingkiran minyak silikon intraokular: Penentuan masa, hasil, dan penemuan komplikasi minyak silikon

Abstrak

Pengenalan: Minyak silikon adalah agen tamponad pilihan yang digunakan dalam vitrectomy pars-plana untuk masalah retina lekang apabila kesan tamponade dari dalam diperlukan untuk jangkamasa yang panjang. Disebabkan kemungkinan komplikasi jangka panjang, penyingkiran minyak silikon (ROO) adalah disyorkan.
Tujuan: Kajian ini dilakukan untuk menilai jangka masa dan komplikasi minyak silikon tamponad, dan hasil anatomi dan tahap penglihatan selepas penyingkiran minyak silikon.
Reka bentuk kajian: Kajian retrospektif.
Bahan dan kaedah: Kajian retrospektif dilakukan kepada 55 mata daripada 55 orang pesakit, yang mana ROO telah dijalankan di Hospital Sultanah Bahiyah pada tahun 2016 dengan tempoh enam bulan susulan selepas pembedahan.
Keputusan: Tempoh tamponad minyak silikon di dalam mata ini antara 1.0 hingga 55.5 bulan, dengan jangka masa purata 10.8 bulan (SD 7.74). Komplikasi biasa minyak silikon tamponad yang diperhatikan adalah katarak dalam 30 mata (54.5%), diikuti oleh tekanan tinggi intraokular sekunder dalam 6 mata (10.9%), dan keratopati band dalam 3 mata (5.5%). Enam mata (10.9%) mengalami lekang retina semula selepas penyingkiran minyak. Majoriti mata dalam kumpulan melekat secara anatomi selepas ROO (40 mata, 81.6%) menunjukkan peningkatan ketajaman penglihatan, dengan penglihatan yang terbaik LogMAR 1.38 (6/150) sewaktu minyak silikon

masih di dalam mata ke tahap LogMAR 0.88 (6/48) pada susulan terkini.
Kesimpulan: Walaupun jangka masa yang disyorkan minyak tamponade silikon adalah antara tiga hingga enam bulan, masa optimum untuk penyingkiran minyak silikon masih tidak diketahui. ROO disyorkan kerana komplikasi yang berkaitan dengan minyak, tetapi keberkesanan terhadap hasil anatomi harus diambil kira. Walau bagaimanapun, dalam keadaan kekangan sumber dan masa terhad yang kami hadapi, ditambah pula peningkatan ketara jumlah pesakit yang memerlukan pembedahan minyak silikon, adalah mustahil untuk mematuhi masa secara tepat yang disyorkan untuk ROO, kebiasaannya penentuan masa adalah mengikut keperluan individu.

Kata kunci: katarak, glaukoma, tamponad dalaman, keratopati, vitrectomy pars-plana, lekang retina, minyak silikon

Introduction

There are several tamponade agents available to be used in pars-plana vitrectomy (PPV), but silicone oil is the preferred endotamponade agent if longer duration of tamponade is needed for retinal re-attachment. However, silicone oil can lead to long-term complications such as cataract formation, secondary high intraocular pressure (IOP), and corneal endothelial decompensation.[1-6] Hence, removal of silicone oil (ROO) is recommended once anatomical re-attachment has been achieved.[7] The exact timing for silicone oil removal is still controversial and debatable, as it depends on multiple factors such as stability of the retinal status and complications from the silicone oil itself. Therefore, recommendations range from three to six months in successfully attached eyes.[8,9] Most authors reported an improvement in final visual acuity post-ROO, but it is believed that duration of silicone oil tamponade may have an effect on visual acuity. However, current evidence to support this is lacking. Compared to other tamponade agents, silicone oil is more likely to enhance anatomical re-attachment rates, but its functional outcome is still debatable.

This study was conducted to determine the mean duration and complications of silicone oil tamponade, as well as the anatomical and visual outcomes after silicone oil removal.

Materials and methods

The medical and surgical records of all patients who underwent silicone oil removal from January 1 to December 31, 2016 at Hospital Sultanah Bahiyah (Alor Setar, Kedah, Malaysia) were reviewed. A minimum postoperative follow-up duration of

Table 1. Demographic features, initial indication for PPV, and duration of silicone oil tamponade

Variables	Patients
Demographic feature:	
Total number of patients	55
Males, no. (%)	36 (64.5)
Females, no. (%)	19 (35.5)
Age (years) mean (SD) (range)	52.9 (13.33) (11-75)
Indication for PPV with silicone oil tamponade:	
ADED (combined TRD, RRD affecting macula), no. (%)	31 (56.5)
RRD with PVR, no. (%)	21 (38)
Vitreomacular traction, no.	1
Traumatic endophthalmitis with RD, no.	1
Full thickness macula hole, no.	1
Duration of silicone oil tamponade:	
< 3months, no. (%)	1 (1.8)
3-6 months, no. (%)	7 (12.7)
6-12 months, no. (%)	35 (63.7)
> 12 months, no. (%)	12 (21.8)

PPV: pars-plana vitrectomy; ADED: advanced diabetic eye disease; TRD: tractional retinal detachment; RRD: rhegmatogenous retinal detachment; PVR: proliferative vitreoretinopathy

six months was taken to determine the anatomical and visual outcomes after ROO. Ten eyes from an initial 65 ROO cases performed were excluded from the study for lack of follow-up before the six months appointment.

Out of 55 patients with 55 silicone oil-filled eyes who fulfilled our inclusion and exclusion criteria, 36 were males (64.5%) and 19 were females (35.5%). Subjects' age ranged from 11 to 75 years, with mean age of 52.9 years. The demographic features of the analysed eyes are shown in Table 1.

The two common indications for using silicone oil as tamponade agent during PPV were:

1. advanced diabetic eye disease (ADED) with combination of tractional (TRD) and rhegmatogenous retinal detachment (RRD) affecting the macula (n = 31, 56.5%); and
2. proliferative vitreoretinopathy (PVR) from RRD (n= 21, 38%).

The rest of the indications were listed in Table 1. Silicone oil with 5000 Centistokes (CS) viscosity was used in all of these eyes.

Decision for ROO was made once retinal re-attachment had been achieved anatomically, frequently more than three months after vitrectomy. However, the decision was also made based on the initial indication of silicone oil usage as tamponade agent and any severe complications arising from the oil tamponade requiring early ROO.

Surgeries were done by a qualified vitreoretinal surgeon and two vitreoretinal fellows using either the trans-pupillary or pars-plana sclerotomy approach. Thirty eyes (54.5%) had ROO combined with cataract extraction in the same setting (*i.e.*, phacoemulsification followed by controlled posterior capsulotomy and oil removal via trans-pupillary approach before intraocular lens implantation) due to lack of resources. The remaining 25 eyes (45.5%) had ROO via pars-plana sclerotomy approach.

Statistical analysis was performed on the extracted data using the two-sample t-test and simple linear regression test. A p-value of less than 0.05 was set for statistical significance.

Results

Duration of silicone oil tamponade in these 55 eyes ranged from 1 to 55.5 months, with a mean duration of 10.85 months (SD 7.74). We divided the duration of oil tamponade into four categories: less than 3 months, 3 to 6 months, 6 to 12 months, and more than 12 months. The majority had an oil tamponade for 6 to 12 months (n = 35, 63.7%), as shown in Table 1.

Of the 55 eyes that were anatomically attached during preoperative assessment for ROO, 6 eyes (10.9%) developed retinal re-detachment after oil removal (Table 2). The mean duration of silicone oil tamponade in eyes that remained attached post-operatively was 11.0 months (SD 8.0), but was shorter (9.4 months [SD 5.2]) in the re-detached group. The difference of mean duration between these two groups was investigated using the two-sample t-test, which appeared not significant (Table 3). The simple linear regression test was used to find out any correlations between duration of silicone oil tamponade and re-detachment rates after ROO, but the result was not significant (Table 3). Most re-detachment occurred in eyes with PVR (66.7%, n = 4). The earliest re-detachment occurred at day 1 after ROO in a case of poor prognosis with 19.5 months of silicone oil tamponade duration for post-traumatic endophthalmitis and RD complicated with band keratopathy. The latest re-detachment occurred four months after ROO due to severe PVR changes in an eye with a giant retinal tear.

The complications of silicone oil tamponade observed in this study are listed in Table 2. The most common complication was cataract formation (54.5%, n = 30),

Table 2. Complications of silicone oil tamponade, anatomical and visual outcome after ROO

Variables	Patients
Anatomical outcome after ROO:	
Attached, no (%)	49 (89.1)
Re-detached, no. (%)	6 (10.9)
ADED with combined RD, no.	31
Attached, no. (%)	30 (96.8)
Re-detached, no. (%)	1 (3.2)
PVR, no.	21
Attached, no. (%)	17 (81.0)
Re-detached, no. (%)	4 (19.0)
Others, no.	3
Attached, no. (%)	2 (66.7)
Re-detached, no. (%)	1 (33.3)
Complications of silicone oil:	
Cataract, no. (mean duration (months), SD)	30 (9.9, 5.0)
High IOP (mean duration (months), SD)	6 (11.2, 10.9)
Band keratopathy (mean duration (months), SD)	3 (12.8, 5.97)
Emulsified oil (mean duration (months)	1 (12.5)
Visual acuity outcomes after ROO:	
ADED with combined RD, no.	30
Improved vision, no. (%)	24 (80.0)
Unchanged vision, no. (%)	3 (10.0)
Worsening vision, no (%)	3 (10.0)
PVR, no.	17
Improved vision, no. (%)	14 (82.4)
Unchanged vision, no. (%)	2 (11.8)
Worsening vision, no (%)	1 (5.8)
Others, no.	2
Improved vision, no. (%)	2 (100.0)
Unchanged vision, no. (%)	n/a
Worsening vision, no (%)	n/a

n/a: non-applicable; PPV: pars-plana vitrectomy; ADED: advanced diabetic eye disease; TRD: tractional retinal detachment; RRD: rhegmatogenous retinal detachment; PVR: proliferative vitreoretinopathy

Table 3. Association between re-detachment rate after ROO with duration of silicone oil tamponade

	Attached retina	Re-detached retina	P-value
Patients, no.	49	6	
Duration of tamponade:			
Range (months)	1–55.5	5.5–19.5	0.636
Mean (months, SD)	11.0 (8.0)	9.4 (5.2)	0.793

Table 4. Association between visual acuity before ROO and visual outcome after ROO with duration of silicone oil tamponade

	Vision before ROO	Visual outcome after ROO
Range (LogMAR)	0.3-2.6	0.2-2.9
Mean (LogMAR, SD)	1.38 (0.64)	0.88 (0.53)
P-value	0.722	0.507

with mean tamponade duration of 9.9 months (SD 5.0). Six (10.9%) of these eyes developed secondary high IOP with mean tamponade duration of 11.2 months (SD 10.9). Three eyes (5.5%) developed band keratopathy; mean duration of oil tamponade in these eyes was longer, 12.8 months (SD 5.97). All of them underwent chelation of band keratopathy in the same setting of ROO, but the condition persisted postoperatively, and no further chelation was planned.

Visual acuity outcomes after ROO excluding eyes with re-detachment are summarised in Table 2. This was determined by comparing the best corrected visual acuity at the last follow-up visit after ROO with preoperative visual acuity. Improvement of vision of at least 1 line using the Snellen chart was considered as visual improvement, while worsening of vision was defined as a drop of at least 1 line using the Snellen chart. The majority (40 eyes, 81.6%) showed improvement in vision regardless of the underlying ocular problem. Overall, the mean visual acuity of these eyes with silicone oil in situ was LogMAR 1.38 (6/150), while the mean at last follow-up visit was LogMAR 0.88 (6/48). There was no statistically significant correlation between visual acuity before ROO and visual improvement after ROO with duration of silicone oil tamponade, as shown using the simple linear regression test (Table 4).

Discussion

In this study, the mean duration of silicone oil tamponade was 10.85 months (SD 7.74). The majority had an oil tamponade duration of 6 to 12 months (n = 35, 63.6%). The shortest duration was one month, as early ROO was done due to uncontrolled high IOP with persistent vitreous haemorrhage. The longest duration was 55.5 months, in which the patient had the operation done at a different centre and defaulted follow-up for a few years before he was referred to us. Timing of ROO has no significant effect on the re-detachment rate in our study. Re-detachment occurred in 10.9% (n = 6) of the eyes and mostly (n = 4) in eyes with PVR changes. There was no specific timing reported for oil removal, but some authors recommended that it should ideally be done if the retina is anatomically stable in the surgeon's opinion.[9-13] Having said that, there are other factors that affect the decision for timing of ROO, such as causes and severity of retinal detachment before surgery and complications arising from the silicone oil itself (*i.e.*, uncontrolled IOP, emulsified oil).

Various mechanisms of action have been postulated on how silicone oil can cause complications in the eye. More than half of our patients (54.5%) developed or had worsening cataract with silicone oil, hence had combined cataract extraction and intraocular lens implantation done in the same setting during ROO. Cataract formation, mainly posterior subcapsular opacity, was observed to occur after intravitreal silicone oil injection and continued to develop even after ROO.[14] The exact mechanism of cataract formation remains unknown, but it is believed to be related to the following factors:

1. bright and prolonged exposure to intra-operative illumination, leading to changes in the transparency of the lens;
2. increase in oxygen tension within the lens, which increases the risk of cataract formation;
3. changes in lens metabolism; and
4. inflammatory reaction.[15]

New research found that, at the molecular level, silicone oil can cause changes in secondary structures of αB-crystallin protein and amyloid-like aggregation, which have been linked with the mechanism of cataract formation.[15]

As is widely known, silicone oil tamponade may cause secondary high IOP. Different mechanisms of raised IOP either due to secondary open or closed angles have been discussed, such as:

1. mechanical obstruction of aqueous humour outflow by silicone oil in the anterior chamber;
2. pupillary block with silicone oil in the anterior chamber,
3. trabecular meshwork obstruction by silicone oil micro-droplets; and
4. inflammation.[16]

A recent study found that the level of inflammatory mediators in aqueous humour were increased in silicone oil-filled eyes with secondary high IOP, suggesting the

involvement of inflammation in its pathogenesis.[17] About 10.9% of our patients had secondary high IOP. Of these, four eyes were controlled with medical treatment alone, one eye was planned for drainage device implantation, and one eye required early oil removal. The silicone oil was removed a month after initial vitrectomy for ADED, as there was uncontrolled IOP secondary to silicone oil with persistent vitreous haemorrhage. After ROO, the patient developed suprachoroidal haemorrhage and subsequently the eye became pthisical.

The other dreaded complication of silicone oil is corneal decompensation and band keratopathy, but the incidence was generally low. Three of our patients developed band keratopathy. They had chelation done at the time of ROO, and the condition was reversible in two eyes. None of them needed keratoplasty. This complication may occur when silicone oil comes in contact with the corneal endothelium, causing a reduction in endothelial cell density and pleomorphism of remaining endothelial cells, hence resulting in corneal oedema and bullous keratopathy, stromal hypercellularity, superficial stromal calcification, and retro-corneal membrane formation.[18]

There are several types of silicone oil being used as a tamponade agent in vitrectomy for complex retinal detachment, the most widely used types being 1000, 2000, and 5000 CS. The decision of which oil to use may depend on surgeon preference. These oils are almost similar in terms of surface tension and specific gravity, but have significantly different molecular weights.[19] Evidence has shown that there was no significant difference in incidence of complications between these silicone oils,[19] but a study reported that high-viscosity silicone oil (5000 CS) is more resistant to emulsification.[20] There are several more silicone oil complications other than the ones mentioned above, but not observed in our study, such as macular pucker formation, cystoid macular oedema, and rubeosis.[21]

Most of our patients (40 eyes, 81.6%) had improved vision after ROO. Removing the silicone oil bubble reduces optical interference, hence resulting in better visual acuity. About half of these patients had cataract extraction done in the same setting as ROO, which may contribute to better visual acuity post ROO.[13] Only a small number of patients experienced unchanged (five eyes) or worsening vision (four eyes). These eyes were those with ADED with vitreous haemorrhage, persistent macular oedema, epiretinal membrane formation, and unhealthy macula with disruption of ellipsoid-myoid junction on optical coherence tomography observed during the post-operative period. Possible mechanisms for worsening vision after silicone oil usage were: optic nerve damage as a result of direct tissue infiltration of SO, generalized macular dysfunction with lesions of ganglion cells and horizontal-bipolar cells, and significant reduction in the inner retinal thickness indicating neuronal cell loss in the macular area.[21] From this study, the duration of silicone oil tamponade does not affect patients' visual acuity before ROO and visual outcome after ROO. However, very few studies have commented on this correlation, but similar findings were reported in Ellen *et al.*[22]

The mean duration of silicone oil tamponade in our study may not truly reflect the intended practice we want to achieve. With limited time and resources as well as increasing number of patients indicated for silicone oil in our setting, it is impossible for us to comply with the recommended time for ROO.

In conclusion, there should be no exact timing for ROO but, if possible, it should be performed within the recommended duration of three to six months. Having said that, surgeons must also evaluate the anatomical stability and oil-related complications before deciding for ROO. Therefore, the timing for ROO should be made on a case-to-case basis. Thorough examination checking for silicone oil complications is mandatory. This is also applied after ROO to identify early signs of re-detachment. Further study should be carried out to identify the risks of re-detachment among patients after ROO. Patients should also be made aware that even though overall visual improvement after ROO is promising, there is a small risk of vision remaining the same or even worsening after the procedure. This outcome depends greatly on the initial anatomical and functional condition of the retina before vitrectomy. With several types of silicone oil available in the market, the search for an ideal intraocular tamponade with long-acting effect but fewer potential complications will continue.

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Brief report

Primary open-angle glaucoma with retinal vein occlusion: a retrospective case series

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Abstract

Glaucoma is a known risk factor for retinal vein occlusion (RVO). There are many reported studies among primary open-angle glaucoma (POAG) patients with RVO in Caucasians. Our objective was to report the natural course of RVO in Asian patients with POAG.

A retrospective record review was conducted between January 2015 and December 2016 involving five POAG patients who developed RVO while attending regular follow-up at the Hospital Universiti Sains Malaysia glaucoma clinic (Malaysia). Three readings of intraocular pressure (IOP) were taken as pre-RVO IOP. IOP at presentation of RVO was also recorded. Clinical data including RVO management and complications were documented.

All POAG patients were at the severe and end stage of the disease. None of them achieved target pressure. Median IOP at presentation was 26 ± 3.8 mmHg (SD) and the majority were asymptomatic. Systemic hypertension was present in all patients. There was deterioration of visual acuity and increased number topical medication post RVO presentation. Vigilant monitoring of IOP is important in POAG patients with systemic hypertension to prevent RVO, given that RVO in POAG is like robbing someone blind twice.

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Keywords: glaucoma, ocular hypertension, intraocular pressure (IOP), retinal vein occlusion (RVO)

Siri kes retrospektif: Glaukoma sudut terbuka Primer dengan oklusi vena retina

Abstrak

Glaukoma adalah faktor risiko yang sudah diketahui bagi oklusi vena retina (RVO). Terdapat banyak kajian yang dilaporkan dalam kalangan pesakit glaukoma sudut terbuka utama (POAG) dengan RVO di Caucasians. Objektif kami adalah untuk melaporkan rantaian semula jadi RVO dengan POAG dalam kalangan pesakit di Asia.

Kajian semula rekod secara retrospektif telah dijalankan antara Januari 2015 dan Disember 2016 yang melibatkan lima pesakit POAG yang mengalami RVO semasa menjalani pemeriksaan ulangan di klinik glaukoma Hospital Universiti Sains Malaysia (Malaysia). Tiga bacaan tekanan intraokular (IOP) telah diambil sebagai pra-RVO IOP. IOP semasa peristiwa RVO berlaku juga direkodkan. Data klinikal termasuk pengurusan RVO dan komplikasi telah didokumenkan.

Semua pesakit POAG ini berada pada tahap teruk dan akhir bagi penyakit glaukoma. Tiada seorang pun daripada mereka yang mencapai tekanan sasaran. Median IOP pada detik peristiwa CVO berlaku adalah 26 ± 3.8 mmHg (SD) dan majoriti adalah tidak menunjukkan sebarang gejala. Semua pesakit mengidap Hipertensi sistemik. Terdapat kemerosotan ketajaman penglihatan dan peningkatan jumlah ubat-ubatan topikal selepas berlakunya RVO. Bagi mencegah RVO, kawalan ketat terhadap IOP adalah penting dalam kalangan pesakit POAG yang juga pengidap hipertensi sistemik. Pesakit POAG yang mengalami RVO boleh diibaratkan seperti merampas deria penglihatan mereka sebanyak dua kali.

Kata kunci: glaukoma, hipertensi okular, tekanan intraokular (IOP), oklusi urat retina (RVO)

Introduction

The association of retinal vein occlusion (RVO) and primary open-angle glaucoma (POAG) has been a subject of interest since 1913.[1] Most studies found a positive association between RVO and uncontrolled intraocular pressure (IOP) in glaucoma or ocular hypertension (OHT) patients.[2-4] Based on the Beaver Dam Eye Study,

glaucoma was found to increase the risk of central retinal vein occlusion (CRVO) 10.7 fold (95% CI 3.74, 30.67).[5] The incidence of RVO in glaucoma and OHT has been reported between 10% and 16%, respectively.[2,6,7] The incidence of RVO in the Ocular Hypertension Study (OHTS) was 1.4% over 9.1 years of follow-up.[8]

The OHTS found that the incidence of RVO in the non-treated group was higher than in the treated group, but without statistically significant difference.[8] On the contrary, there was no direct relationship between IOP and RVO in glaucoma patients.[9] There were also reported cases of asymptomatic RVO in glaucoma patients.[10] To complicate matters, it was found that the contralateral eye progressed faster in bilateral glaucoma patients with unilateral BRVO.[11] In addition, thinner retinal nerve fibre layer (RNFL) thickness was detected in the contralateral eye with unilateral RVO.[9] Detection and follow-up is important in glaucoma patients with RVO.

Most studies reported cases of Caucasians with RVO in POAG. There is minimal evidence in Asians.[12] Several studies conducted in different Asian countries showed variations in RVO prevalence, which may be due to racial, environmental, or methodological differences.[12] Understanding the natural course of RVO in Asian patients with POAG is important in planning an effective strategy for blindness prevention in the Asian region. The aim of this report was to study the natural course of RVO in Asians patients with POAG.

Materials and methods

A retrospective record review was conducted on POAG patients who attended the glaucoma clinic at the Hospital Universiti Sains Malaysia (Kelantan, Malaysia) between January 2015 and December 2016. POAG patients who were on regular follow-up were included. POAG was diagnosed based on structural and functional criteria according to the World Glaucoma Consensus.[13] Those who were not known to have POAG during RVO presentation or POAG diagnosed after RVO presentation were excluded. Those who developed RVO due to other causes, such as systemic blood disorder, were also excluded. Blood investigations such as full blood panel and erythrocyte sedimentation rate were conducted. Patients with more than 30% of missing data were also excluded. A total of ten POAG patients with RVO were identified. However, three patients were excluded due to unclear status of POAG diagnosis and another two patients due to having more than 30% of missing data.

The diagnosis of ischemic or non-ischemic RVO was based on clinical presentation: visual acuity, presence of relative afferent pupillary defect, iris neovascularization, and fundus findings (degree and extent of retinal haemorrhage, cotton wool spots, degree of retinal vessel dilatation and tortuosity, and presence of collaterals or neovascularization).[14] RVO includes CRVO, hemiretinal vein occlusion (HRVO), and BRVO.[15]

Data extracted from the medical records includes demographic data, clinical presentation of both POAG and RVO, and management, including the final visual

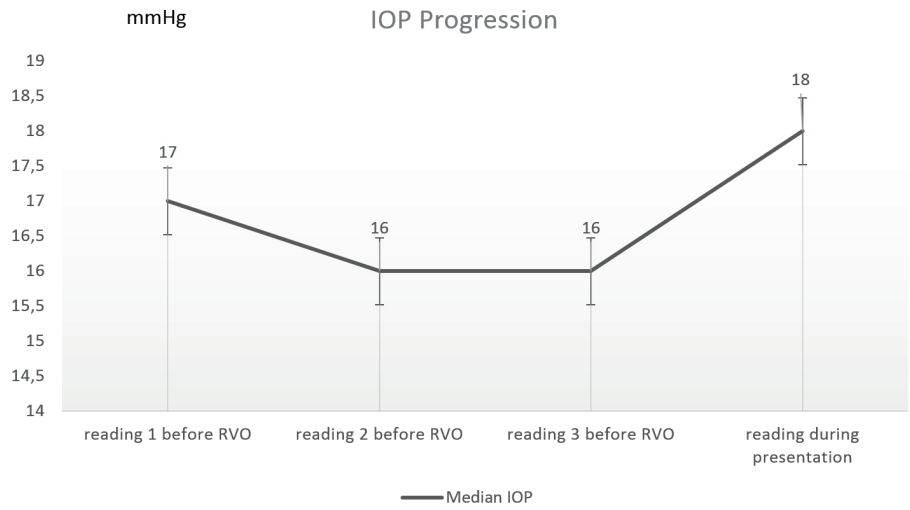

Fig. 1. Median IOP at RVO presentation and three IOP readings pre-RVO.

outcome. These include three consecutive IOP measurements taken prior to RVO presentation (during POAG follow-up period), known in this study as pre-RVO IOP. IOP was measured using Goldmann applanation tonometry. Visual acuity was recorded at RVO presentation and the latest follow-up. Complications, such macular oedema, and RVO and POAG management, including investigating other possible causes of RVO, was also documented. Median IOP was calculated at RVO presentation and three consecutive visits prior to development of RVO.

Results

Five subjects were included in this study: two men and three women, with a mean age of 70 ± 3.7 years (SD) (Table 1). Systemic hypertension was present in all subjects (Table 1). Based on clinical presentation, three developed CRVO, one developed HRVO, and one developed BRVO (Table 1). In Case 2, RVO developed in an already blind eye (NPL) due to POAG.

IOP measurements ranged between 17 mmHg and 26 mmHg at presentation (Table 2). There was an increasing trend of IOP prior to RVO presentation but none reached above 20 mmHg (Fig. 1). The highest IOP at presentation of RVO was 26 mmHg (Table 2). Clinical evidence of neovascularization is absence except for Case 4 (Table 2). There was an increase in the number of pressure-lowering drugs required post RVO in all subjects except for Case 2. Two subjects developed macular oedema requiring intravitreal ranibizumab injection.

Table 1. Summary of patient characteristics at presentation RVO

Case	Age	Sex	Ethnicity	Duration POAG (months)	Type of RVO/ Laterality	Type	Systemic Disease	BCVA During RVO		VCDR	
							Hypertension	OD	OS	OD	OS
1	70	F	Chinese	36	CRVO OD	ischemic	Yes	6/12	6/6	0.8	0.7
2	74	M	Chinese	9	CRVO OS	ischemic	Yes	6/30	NPL	0.9	1.0
3	71	M	Malay	24	CRVO OS	ischemic	Yes	6/7.5	CF	0.6	0.9
4	64	F	Malay	15	BRVO OS	ischemic	Yes	6/15	CF	0.9	0.95
5	71	F	Malay	72	HRVO OD	non ischemic	Yes	6/24	6/7.5	0.6	0.8

M: male; F: female; RVO: retinal vein occlusion, CRVO: central retinal vein occlusion; BRVO: branch retinal vein occlusion; HRVO: hemiretinal vein occlusion; OD: right eye; OS: left eye; VCDR: vertical cup-to disc-ratio; BCVA: best corrected visual acuity; CF: counting finger; NPL: no perception to light

Table 2. Summary of ocular findings and management of RVO

IOP pre-RVO and RVO										Management and final outcome						
Case	**RVO**	**IOP (1st pre-RVO)**		**IOP (2nd pre-RVO)**		**IOP (3rd pre-RVO)**		**IOP (at presentation)**		**NV Present**	**PRP**	**Macular oedema**	**Number of glaucoma medications**		**Final BCVA**	
		OD	OS	OD	OS	OD	OS	OD	OS				Pre-RVO	Post-RVO	OD	OS
1	OD CRVO	17	19	26	18	20	16	26	20	NO	YES	YES	3	4	HM	6/6
2	OS CRVO	10	12	12	10	38	40	20	22	NO	YES	NO	3	1	HM	NPL
3	OS CRVO	18	16	14	18	14	14	16	18	NO	NO	YES	4	4	6/6	3/60
4	OS BRVO	14	15	18	26	14	16	16	18	YES	YES	NO	2	4	6/6	PL
5	OD HRVO	18	13	14	14	16	14	17	16	NO	YES	NO	1	2	6/9	6/6

RVO: retinal vein occlusion, BRVO: branch retinal vein occlusion; HRVO: hemiretinal retina vein occlusion; OD: right eye; OS: left eye; IOP: intraocular pressure; NV: new vessel; PRP: panretinal photocoagulation; VA: visual acuity, BCVA: best corrected visual acuity; HM: hand movement; CF: counting finger; NPL: no perception to light

Discussion

Most POAG patients who developed RVO were at advanced and end stage (based on VCDR) and none of them achieved target pressure based on the three readings of pre-RVO IOPs. However, the median IOPs pre-RVO did not reach more than 20 mmHg. In fact, there was a slight reduction in median IOP prior to RVO presentation. Due to the retrospective nature of the study, the measurement of IOP pre-RVO presentation was not standardized in terms of intervals and times taken. Diurnal IOP variation was not addressed.

IOP elevation is believed to be the risk factor for RVO due to compression and collapse of the central retinal vein.[1] In pre-existing glaucoma, IOP at CRVO presentation was higher with a mean of 21.7 mmHg compared to the non-pre-existing glaucoma group (13.9 mmHg).[16] In this study, the highest recorded IOP during RVO presentation was 26 mmHg, due to all patients being on topical lowering-pressure drugs. Currently, IOP elevation is no longer exponentially related to RVO.[2] Furthermore, there was no statistically difference in RVO prevalence between treated and non-treated OHT patients.[8] Mean IOP of OHT with BRVO was slightly higher than OHT without RVO, but was not statistically significant.[17] However, no studies show that reaching target IOP prevents RVO or prevents RVO in the contralateral eye in pre-existing POAG/OHT with RVO.

Systemic hypertension has a strong correlation with RVO and open-angle glaucoma.[18] In our case series, systemic hypertension was present in all cases. It has been reported that 60% of RVO patients were hypertensive patients.[19] According to Hayreh *et al.*, there was a significantly higher prevalence of arterial hypertension in BRVO compared with CRVO and HRVO.[20] However, there are no studies so far showing a pressure trend before the development of RVO. We have not documented blood pressure control in our subjects. In addition, increasing age is exponentially related to the prevalence of both diseases.[18] The median age was 71 years old in this series. Perhaps, there is a connection between age, systemic hypertension, and these two blinding ocular diseases: RVO and POAG.

All our patients demonstrated deterioration of visual acuity post RVO except for Case 5. Good visual acuity in this patient was likely due to non-ischaemic HRVO without macular involvement. Final visual acuity outcome was affected by the type of RVO.[21] Non-ischaemic RVO has better visual prognosis.[21] However, 34% of non-ischemic CRVO can convert to ischemic type within three years.[14,22] Interestingly, none of the subjects developed clinical evidence of neovascularization except for Case 4 with BRVO. Varying degrees of retinal ischaemia due to non-perfusion of retinal capillaries may occur depending on the degree of retinal vein thrombosis.

Standard treatment of the underlying ischemia in RVO includes panretinal photocoagulation (PRP) combined with medical and surgical management for elevated IOP. According to the Central Retinal Vein Occlusion Study Group, PRP should be performed promptly at the first sign of definite neovascularization, but not pro-

phylactically.[7] However, PRP was performed in cases without definite neovascularization in our present case series, not as prophylactic treatment, but due to a high tendency to default follow-up, as they were living in another state. PRP was initiated earlier due to higher risk of ischaemic CRVO to develop neovascular glaucoma, which may lead to more challenging complications.[23] Currently, intraocular injection of anti-vascular endothelial growth factor has gained popularity in RVO treatment. Several studies have shown its effectiveness in preventing the complications arising from neovascularization.[24,25] However, this treatment is expensive and requires multiple injections. We reserved this injection as pre-treatment prior to surgical interventions such as glaucoma drainage device implantation.

This retrospective case series may not be the best to reflect RVO in POAG. However, based on this case series, target pressure should be achieved in POAG patients, especially those with systemic hypertension. To the best of our knowledge, there is no recommended target IOP or blood pressure to prevent RVO in POAG. Perhaps, strict monitoring of IOP and blood pressure in POAG patients with systemic hypertension may help prevent the development of RVO.

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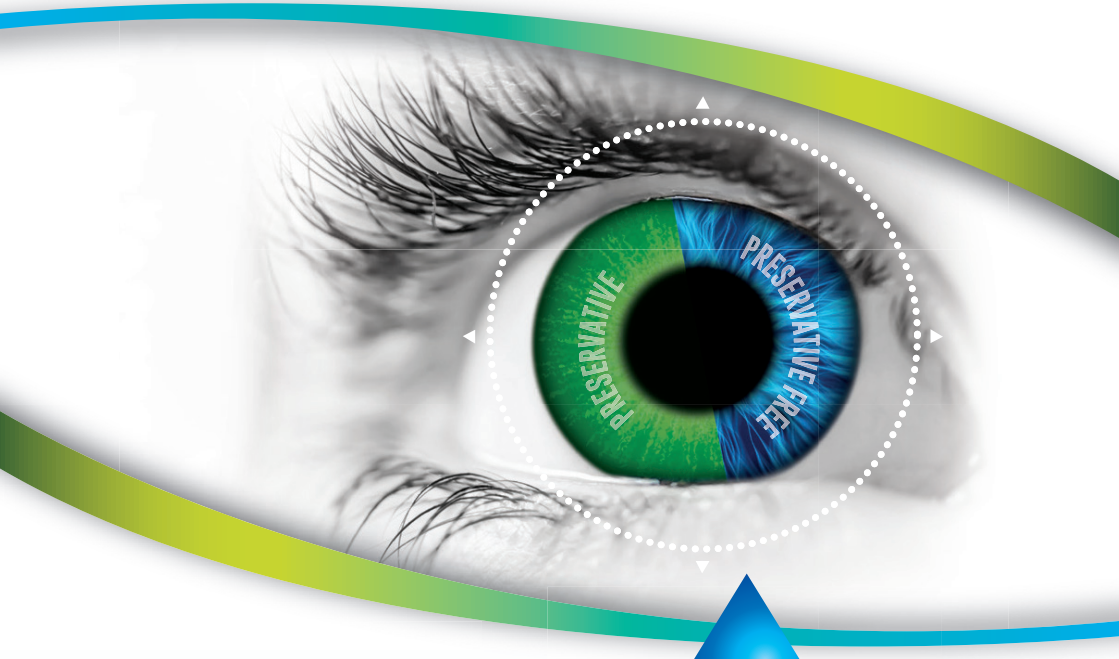

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Case report

Reversal of impending central retinal vein occlusion secondary to hyperleukocytosis in chronic myeloid leukemia by leukapheresis: a case report

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Abstract

We report an uncommon case of bilateral impending central retinal vein occlusion (CRVO) in a young girl with newly diagnosed chronic myeloid leukaemia (CML) and its successful reversal with leukapheresis. A young girl presented with vomiting and fever. Examination revealed hepatosplenomegaly and multiple enlarged lymph nodes. Investigations show severe hyperleukocytosis and anaemia. Bone marrow aspirate and trephine biopsy confirmed CML in the chronic phase. She was promptly referred to the ophthalmology team for assessment of vasculopathy. Bilateral fundus showed swollen and hyperaemic optic discs. There were dilated and tortuous retinal venules with perivascular white cell extravasation, scattered intraretinal haemorrhages, and Roth spots at mid-periphery. She received four cycles of leukapheresis and, consequently, her leukocytes reduced dramatically with associated significant improvement in fundus findings.

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This case highlights uncommon impending CRVO in a young girl and the dramatic improvement in fundus signs following leukapheresis that halted and reversed the progression of impending CRVO.

Keywords: central retinal vein occlusion, chronic myeloid leukaemia, leukapheresis

Pemulihan semula oklusi vena retinal utama ekoran daripada hiperleukositosis dalam leukemia myeloid kronik melalui rawatan leukapheresis

Abstrak

Kami melaporkan kes luar biasa berlaku pada seorang gadis muda, pengidap leukemia myeloid kronik (CML) yang hampir mengalami oklusi vena retinal utama (CRVO) pada kedua-dua belah mata, dan berjaya dipulihkan semula melalui rawatan leukapheresis. Seorang gadis muda mengalami demam dan muntah. Pemeriksaan mendedahkan hepatosplenomegali dan pembengkakan beberapa nodus limfa. Penyiasatan menunjukkan hyperleukocytosis yang teruk dan anemia. Pemeriksaan sumsum tulang dan biopsi trephine mengesahkan CML dalam fasa kronik. Beliau segera dirujuk kepada oftalmologi untuk pemeriksaan lanjut. Fundus pada kedua-dua mata menunjukkan cakera optik yang bengkak dan hiperemik. Terdapat venul retina yang mengembang dan bergelung-gelung serta limpahan sel putih perivascular dengan pendarahan intraretinal, dan bintik Roth pada fundus di bahagian antara pusat dan pinggiran. Beliau menerima empat kitaran leukapheresis dan hasilnya jumlah leukosit berkurangan secara ketara, seterusnya menunjukkan pemulihan yang ketara pada fundus.

Kes CRVO pada seorang gadis muda ini bukanlah kes yang lazim berlaku di mana pemulihan ketara pada fundus berikutan rawatan leukapheresis , yang akhirnya merencatkan dan memulihkan semula CRVO yang hampir berlaku.

Kata kunci: oklusi vena retinal utama, leukemia myeloid kronik, leukapheresis

Introduction

Venous occlusive disease of the retina is the second most common retinal vascular disorder after diabetic retinopathy.[1] Central retinal vein occlusion (CRVO) represents a large subset of venous occlusive disease of the retina and one of the major causes of severe vision impairment. It occurs due to thrombosis of the central retinal vein at

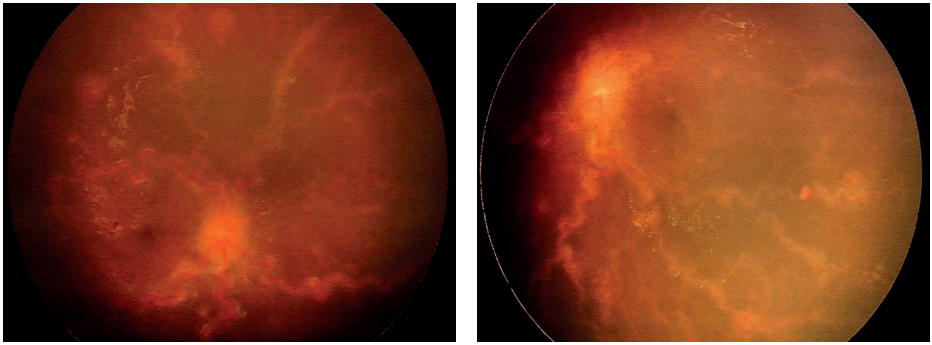

Fig. 1. Fundus pictures of both eyes taken with RetCam showing bilateral dilated, tortuous retinal veins, intraretinal haemorrhages, and a few preretinal haemorrhages. There is also marked optic disc swelling and perivascular white cell extravasation near to optic disc.

the level of the lamina cribrosa. CRVO can be divided into non-ischemic and ischemic varieties based on clinical and fluorescein angiography features.[1] Impending CRVO (also known as incipient, partial, or incomplete CRVO) is an arbitrary term used to describe asymptomatic patients or patients with amaurosis fugax with mild dilated, tortuous retinal veins and few widely scattered retinal haemorrhages.[2] Common risk factors for the development of CRVO include aging, smoking, obesity, atherosclerosis, hypertension, diabetes mellitus, hyperlipidaemia, raised intraocular pressure, and autoimmune disorders. In young patients, uncommon risk factors such as myeloproliferative disorders, congenital or acquired hypercoagulable states, and inflammatory disease associated with occlusive periphlebitis should be considered.[1]

Methods

Case report.

Results

A previously healthy 13-year-old Malay girl was referred to eye casualty with vomiting for two days and fever. There was no altered bowel habit, abdominal pain, appetite loss, nor weight loss. There is no history of malignancy in family. Past ocular history and social history were insignificant.

Upon general examination, there was pallor and multiple enlarged lymph nodes at supraclavicular and inguinal region. Systemic examination revealed normal lungs and cardiovascular system. However, abdominal examination showed presence of

Table 1. Pertinent blood investigation results

Investigations	Results
WBC	728.1 x 10^9/L
HB	6.9 g/dl
Platelet	265 x 10^9/L
C-reactive protein	0.62 mg/dl
Liver function test	Normal
Renal profile Sodium Potassium Urea Creatinine	 137 mmol/L 2.7 mmol/L 3.5 mmol/L 74.9 mmol/L
WBC after 4 cycles of leukapheresis	163.6 umol/L

massive hepatosplenomegaly. At presentation, she was having tachycardia with a heart rate of 130 beats/minute and temperature of 38.8°C.

A battery of tests was conducted and early results raised suspicion of haematological malignancy. She was promptly referred to the ophthalmology team for assessment of retinopathy or vasculopathy associated with haematological malignancy. She denied any visual symptoms and her visual acuity was 6/6 OU with no relative afferent pupillary defect. Her anterior segment examination and intraocular pressure were unremarkable. Bilateral fundus showed swollen and hyperaemic optic discs. There were markedly dilated and tortuous retinal venules with peculiar perivascular white cell extravasation, scattered intraretinal haemorrhages, and Roth spots at mid-periphery. The macula was normal and there was no neovascularization either on the retina or iris (Fig. 1).

Bone marrow aspirate and trephine biopsy confirmed chronic myeloid leukaemia (CML) in the chronic phase. Other investigation results are tabulated in Table 1. She was immediately started on cytoreduction therapy with hydroxyurea, cytarabine, and four cycles of leukapheresis. Subsequently, her leukocytes reduced dramatically to normal levels with accompanying significant improvement in fundus findings. The retinal vessels became progressively less tortuous and dilated, with resorption of perivascular leukocytes and improvement in optic disc swelling.

One month later, the retinal vessels were no longer dilated and tortuous, with complete resolution of retinal haemorrhages and marked reduction of optic disc swelling (Fig. 2). The impending CRVO was completely reversed with rapid instigation of treatment.

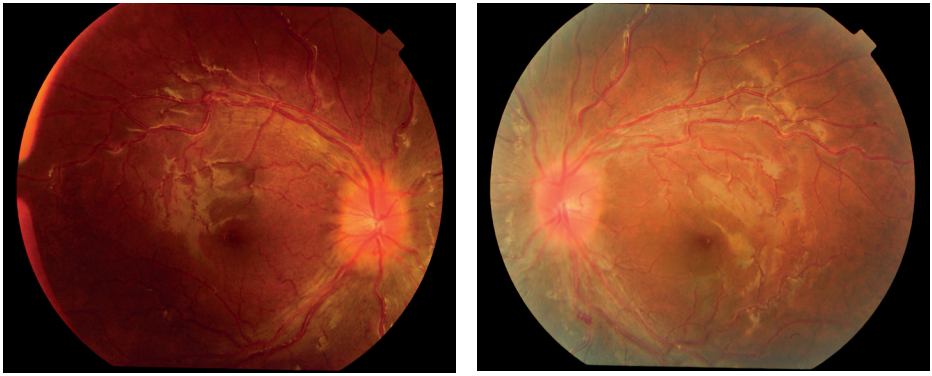

Fig. 2. Fundus pictures of the right eye (*right*) and left eye (*left*) taken two weeks post-leukapheresis shows complete resolution of retinal veins and marked reduction in optic disc swelling. Macula is normal and retinal haemorrhages have mostly resolved.

Discussion

CRVO is an important cause of painless visual impairment. It commonly presents as unilateral in 90% of cases and may later involve the fellow eye to become bilateral in 10% of cases if there is no intervention on the risk factors. Simultaneous bilateral CRVO is a rare clinical entity, presenting in less than 1% of cases.[1] It is commonly associated with elderly patients. However, it may occur in young people with haematological malignancy, as highlighted in this case.

CML is a myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line in bone marrow and spill over into the blood stream. CML has three phases, increasing in severity: chronic phase, accelerated phase, and blast crisis.[3] This patient presented with CML in the chronic phase, which is early-phase in CML. Hyperleukocytosis, which is a feature of CML, is defined as a white blood cell (WBC) count of more than > 100 x 10^9/L. Critical hyperleukocytosis can cause leukostasis, a life-threatening condition with disturbed microcirculation caused by occlusion of small vessels due to elevated blast cell count, endothelial adhesion of myeloid blasts, and tissue infiltration.[4] Leukostasis leads to decreased tissue perfusion, especially in the brain and lungs, leading to a high fatality rate.[5] In view of this, a rapid reduction of WBC is thought to be the mainstay of treatment. This is achieved by cytoreduction through combination of chemotherapy and leukapheresis.

Leukapheresis is a therapeutic procedure that separates WBC from blood and reduces the leukocyte count in patients with symptomatic or threatening leukostasis until induction chemotherapy works.[6] This procedure rapidly reduced the leukocyte count and improved leukostasis in our patient. Consequently, this improved blood flow throughout the body, including the retina, thus restoring normal perfusion.

Eventually, the progression of CRVO was successfully arrested and reversed, hence preventing visual impairment.

Conclusion

This case highlights the dramatic improvement in fundus with swift cytoreduction and remedial measures that halted and reversed the progression of impending CRVO. In view of the restricted availability of leukapheresis treatment, early referral to a centre with leukapheresis facility would save the patient's life and vision.

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Case report

Bilateral optic neuritis secondary to presumed ocular tuberculosis in immunocompetent adults

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Abstract

This case series aims to discuss cases of bilateral optic neuritis secondary to presumed ocular tuberculosis (TB) in two immunocompetent adults. Ocular TB has been associated with optic neuritis, but bilateral cases in immunocompetent individuals are rarely seen. We report a case series of two young healthy adults with bilateral painless optic neuritis as the presenting feature of ocular TB. Clinical examination, TB tests, and angiographic studies supported the diagnosis. All patients were started on anti-TB medication followed by oral prednisolone and had visual improvement a few weeks after treatment. As a conclusion, these cases highlight an atypical case of ocular TB presentation in immunocompetent individuals and thorough investigation is pertinent to preserve the visual function.

Keywords: immunocompetence, ocular tuberculosis, optic neuritis

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Neuritis optik bilateral akibat tuberkulosis okular andaian dalam kalangan orang dewasa yang immunokompeten

Abstrak

Siri kes ini bertujuan untuk membincangkan kes-kes neuritis optik bilateral akibat tuberkulosis okular (TB) andaian dalam dua orang dewasa yang immunokompeten. TB okular selalunya dikaitkan dengan neuritis optik tetapi kes bilateral dalam individu immunokompeten adalah jarang dilihat. Kami melaporkan kes dua orang dewasa yang sihat tetapi mengalami neuritis optik bilateral yang tidak menyakitkan sebagai manifestasi TB okular. Pemeriksaan klinikal, ujian TB, dan kajian angiografi menyokong diagnosis. Semua pesakit dirawat dengan ubat antituberkulosis diikuti dengan ubat prednisolon oral dan pesakit mengalami kesan pemulihan penglihatan dalam masa beberapa minggu selepas rawatan. Sebagai kesimpulan, kes-kes ini memaparkan manifestasi TB okular yang jarang berlaku dalam kalangan individu dewasa yang immunokompeten dan siasatan menyeluruh adalah penting untuk memelihara fungsi visual pesakit.

Kata kunci: immunokompeten, tuberkulosis okular, neuritis optik

Introduction

Ocular tuberculosis presenting as optic neuritis has been seen in immunocompromised patients but bilateral cases in immunocompetent individuals are rarely seen. There are several reports regarding bilateral optic neuritis secondary to ocular TB in immunocompromised patients, but we found no report of bilateral tuberculous optic neuritis in immunocompetent patients.[1] In this case series, we report two cases of ocular TB presenting with bilateral optic neuritis in immunocompetent adults.

Materials and methods

Case series.

Results

Case 1

A 24-year-old gentleman presented with rapid progressive bilateral painless blurring of vision for 11 days preceded by 9 days history of high-grade fever. He denied any chronic cough, loss of weight or appetite, night sweats, or contact with others with such symptoms. He had travelled to Indonesia one week prior to the onset of fever.

Visual acuity was counting finger OD and 1/60 OS. Relative afferent pupillary defect (RAPD) was positive OD. The anterior chamber (AC) was quiet. Fundus examination revealed bilateral hyperaemic swollen optic discs (Figs. 1a and 1b) with intraretinal haemorrhage at the macula and grade 1 vitritis. Systemic examinations were normal. Fundus fluorescein angiography (FFA) revealed fluorescein leakage in both optic discs (Figs. 1c and 1d). Colour vision test was normal.

Mantoux test read 15 mm induration. However, erythrocyte sedimentation rate (ESR) was 11 mm/hour and chest X-ray was normal. Blood investigations for hepatitis, HIV, syphilis, and other infectious diseases were normal. Brain and orbit imaging showed no space occupying lesion.

The patient was treated with 4 daily tablets of Akurit (combination of pyrazinamide, ethambutol, isoniazid, and rifampicin) and oral prednisolone 1 mg/kg/day 3 days later. His vision subsequently improved to 6/24 OD and 6/12 OS after 6 weeks of treatment, and further improved to 6/9 OU after 3 months with resolution of disc swelling.

Case 2

A 31-year-old lady presented with painless blurring of vision in OD for two weeks. Relevant past history included recent travel to an area highly endemic for TB. There were no other ocular or systemic symptoms. She also denied contact with others with chronic cough. She had been treated elsewhere with oral prednisolone for 11 days prior to presentation.

Visual acuity was 6/24, N5 OD, and 6/9, N5 OS. RAPD was positive OD. There were occasional AC cells in OD. Optic disc was swollen and hyperaemic with multiple subretinal nodules in OD (Fig. 2a). The superior and inferior disc margin was blurred in OS (Fig. 2b). Systemic examination was unremarkable. Colour vision test was normal.

Initial investigations revealed positive rapid plasma reagin (RPR) with a titre of 1:16, with positive syphilis IgG and IgM and a Mantoux reading of 20 mm. ESR and other infectious screening parameters were not significant. Chest X-ray, brain, and orbital imaging were normal. She was initially treated as ocular syphilis with intravenous C-penicillin 4 mega units. However, a week later her vision worsened to 6/60 N36 OD and 6/36 N8 OS. FFA showed optic disc leakage and choroiditis, but no vasculitic changes OD and

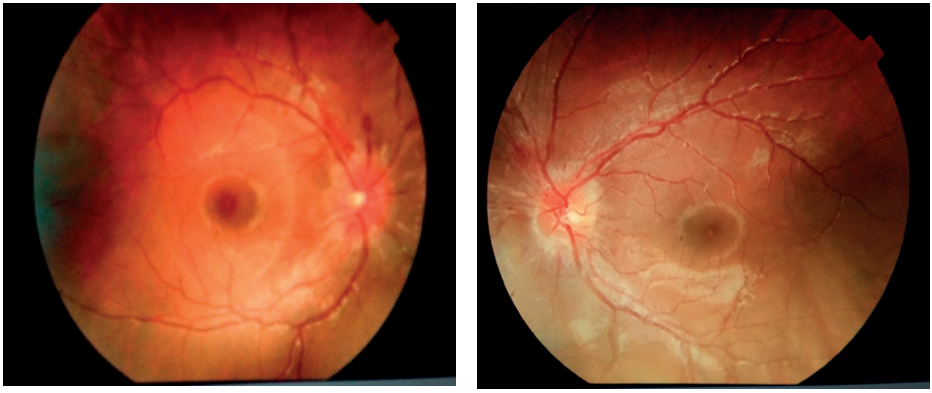

Fig. 1a-b. Colour fundus photograph showing bilateral hyperaemic swollen optic discs with intraretinal haemorrhage at the macula and grade 1 vitritis.

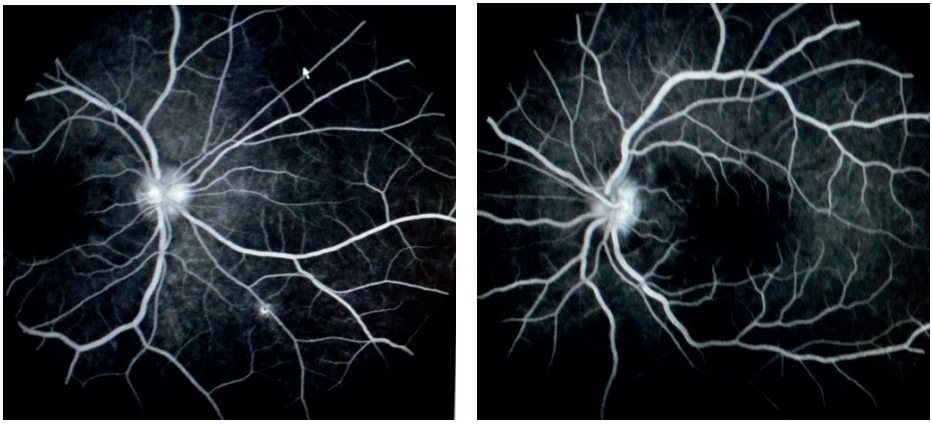

Fig. 1c-d. Fundus fluorescein angiography (FFA) showing fluorescein leakage in both optic discs.

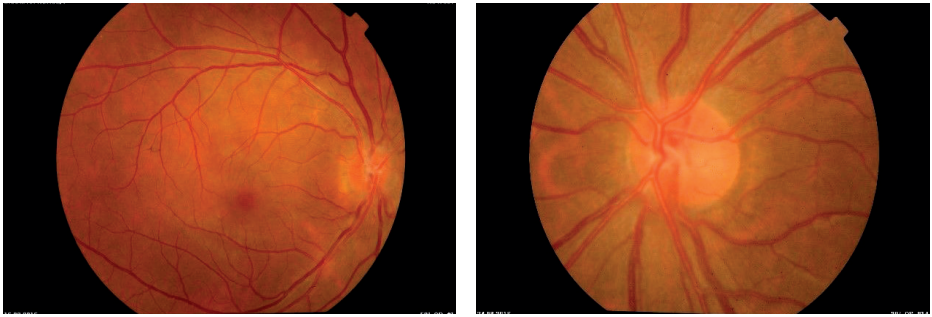

Fig. 2a-b. Colour fundus photograph showing swollen and hyperaemic optic disc with multiple subretinal nodules OD and blurred superior and inferior disc margin OS.

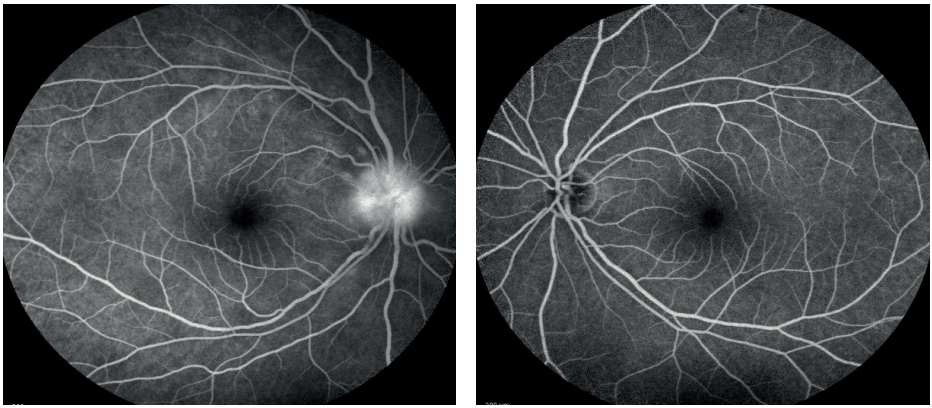

Fig. 2c-d. FFA showed optic disc leakage and choroiditis OD, but no vasculitic changes. No such changes were seen OS.

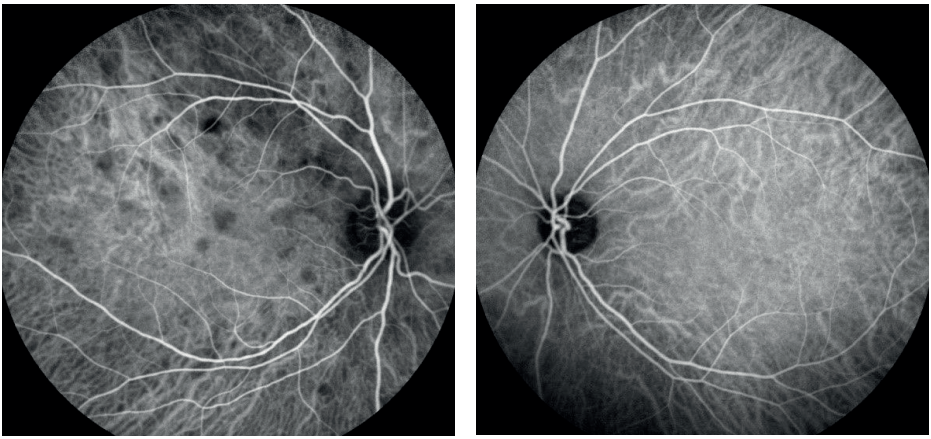

Fig. 2e-2. ICG angiography showed multiple hypofluorescence areas OD, indicating subretinal choroiditis. No such changes were seen OS.

no optic disc leakage OS (Figs. 2c and 2d). Indocyanine Green angiography showed multiple hypofluorescence areas indicating subretinal nodules OD, but no such changes OS (Figs. 2e and 2f). Cerebrospinal fluid was negative for VDRL and TB PCR. The diagnosis was reviewed as ocular TB with systemic syphilis and anti-TB treatment was commenced, followed by oral prednisolone three days later same as the first patient. Her vision improved to 6/9 N6 OU after 3 weeks.

Discussion

Ocular TB is an important cause of infectious uveitis in Southeast Asia. The incidence of ocular TB is variable and is estimated to range from 1.4-5.7%, with a higher percentage in immunocompromised patients.[2]

Ocular TB can result from haematogenous spread, from direct local extension from the skin, mucous membranes, or sinuses, and therefore results in posterior segment involvement such as papillitis, vitritis, retinitis, and choroiditis.[3] In the anterior chamber, it is mostly seen as granulomatous uveitis.[4] In both our cases, the chest X-rays were clear, indicating that these cases were not caused by dissemination from the lungs. In a few cases, ocular TB may occur due to direct entry of *Mycobacterium tuberculosis* into the ocular surface. The pathogenesis of the clinical manifestation is attributed to delayed hypersensitivity reaction.[4]

Definitive testing for TB is often limited and unreliable. Ocular fluid culture or PCR is inadequate due to the small volume and low bacillary concentration. Biopsy is also extremely difficult for lesions in the posterior retina, choroid, or optic nerve. Therefore, diagnosis generally depends on a combination of clinical findings and other supportive tests such as the Mantoux test, TB QuantiFERON, and typical angiographic findings.[5] When used alone, TB QuantiFERON had limited value in differentiating between an acute and latent infection. However, negative TB QuantiFERON and Mantoux tests may allow for exclusion of active TB.[6] In this case, it was also guided by TB medications and the response to it. In both our cases, patients were not keen for TB QuantiFERON testing.

In the second case, the patient had a positive RPR titre that led to an initial diagnosis of ocular syphilis. However, RPR may be falsely positive in tuberculosis, malaria, filariasis, aging, pregnancy, and immunization.[7]

FFA and ICG play an important role in diagnosis. On FFA, active tubercles appear hypofluorescent during the early phase and hyperfluorescent in the later phase. In our second case, initial angiographic studies did not show any changes in the left eye, possibly because the disease was still in its early phase. ICG tends to show lesions better than FFA, in which tuberculous chorioretinitis may remain hypofluorescent in all phases, either atrophic areas or active full-thickness granulomas.[8]

According to Malaysian Clinical Practice Guidelines (CPG), extrapulmonary TB and specifically ocular TB is treated with anti-TB drugs for at least six months. Our

patients were treated with 4 daily tablets of Akurit followed by oral prednisolone 1 mg/kg/day 3 days later. The CPG advocates for use of systemic corticosteroids in tuberculous meningitis and pericarditis.[9] However, steroid therapy in ocular TB is not well documented.[10] Systemic steroids in combination with ATT are occasionally used in patients with persistent ocular inflammation or retinal vasculitis, but there are no clinical trials to prove their efficacy. However, corticosteroids (topical and/or oral) may be used to control the inflammation following the Type IV hypersensitivity reaction. They are generally tapered over 6-12 weeks.[11]

Bilateral tuberculous optic neuritis can occur in healthy young individuals and can be asymmetrical in presentation of blurring of vision. Treatment with the standard anti-TB agents combined with systemic steroids show promising visual outcome. These cases highlight a new trend of ocular TB presentation in immunocompetent individuals and thorough investigation is pertinent to preserve the visual function.

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Case report

Neuroretinitis secondary to dual infection of *Toxoplasma gondii* and *Bartonella hensalae*

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Abstract

A 73-year-old lady with underlying diabetes presented with acute loss of central vision in the left eye. Examination revealed visual acuity of 6/60 in the left eye with positive relative afferent pupillary defect and optic disc swelling with macular oedema. Right eye visual acuity was 6/12 with unremarkable findings. Optical coherence tomography (OCT) showed elevated macular with ceacocentral field defect on Humphrey visual field. Connective tissue screening and tubercular screening were negative. Serological screening for *Toxoplasma sp* and *Bartonella sp* were positive. She was diagnosed as neuroretinitis secondary to both infections and started on oral azithromycin 500 mg once a day and oral corticosteroid. Her final vision improved to 6/12 with normal optic disc and resolved macular oedema.

Keywords: Bartonella hensalae, cat scratch disease, neuroretinitis, *Toxoplasma gondii*

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Neuroretinitis berlaku akibat daripada dua gabungan jangkitan *Toxoplasma gondii* dan *Bartonella hensalae*

Abstrak

Seorang wanita berusia 73 tahun, pengidap diabetes mengadu penglihatannya kabur di bahagian tengah pada mata kiri secara akut. Pemeriksaan menunjukkan ketajaman visual 6/60 pada mata kiri dengan positif kecacatan aferen, cakera optik bengkak dan edema pada makular. Ketajaman visual mata kanan adalah 6/12 dengan penemuan normal. Tomografi koherensi optik (OCT) menunjukkan kawasan makular yang bengkak dengan gangguan medan ceacocentral pada medan penglihatan Humphrey. Pemeriksaan saringan ke atas penyakit tisu konektif dan saringan batuk kering (TB) adalah negatif. Manakala, pemeriksaan serologi untuk *Toxoplasma sp* dan *Bartonella sp* adalah positif. Psakit didiagnosis sebagai mengidap neuroretinitis akibat kedua-dua jangkitan, dan rawatan dengan ubatan azithromycin oral 500 mg sekali sehari dan kortikosteroid oral diberikan. Penglihatannya pulih dan meningkat kepada 6/12 dan menunjukkan cakera optik yang normal dan edema makular yang telah surut.

Kata kunci: Bartonella hensalae, Penyakit cakar kucing, neuroretinitis, *Toxoplasma gondii*

Introduction

Neuroretinitis is a term which refers to the mixture of optic disc swelling and retinal inflammation, typically involving the macula, commonly due to infection with *Bartonella hensalae*, which is a gram-negative intracellular bacterium responsible for cat scratch disease (CSD). Humans get infected via contact with cat fleas, or rarely, cat scratches. Although the diagnosis of CSD may be presumed with clinical criteria, serological evidence of anti *B. hensalae* antibodies is diagnostic.

Ocular toxoplasmosis is caused by *Toxoplasma gondii*, which is an obligate intracellular protozoal parasite which spreads via sporulated oocysts from cats, which are the definitive host. Humans are the intermediate host, and usually get infected transplacentally or through ingestion of undercooked meat containing bradyzoites. The prevalence of toxoplasmosis in Malaysia ranges from 13.9% to 30.2%.[1]

Case report

A 73-year-old lady with diabetes and hypertension presented with acute loss of

central vision in the left eye for 1 week, associated with pain on ocular movement. There was no history of fever, trauma, or headache. She had been scratched by her cat a few months before.

She was afebrile, with normal blood pressure and blood sugar. There were no skin lesions or lymphadenopathy. Visual acuity in the left eye was 6/60, with a positive relative afferent pupillary defect. Fundus examination showed a swollen left disc with an inferior disc haemorrhage. There was macular oedema, which extended to the papillomacular area (Fig. 1). Optical coherence tomography (OCT) revealed intraretinal fluid over the macula extending to the optic disc (Fig. 2). Visual acuity in the right eye was 6/12, with unremarkable findings.

Full blood count, erythrocyte sedimentation rate, renal function test, and liver function test were normal. Tuberculosis screening was negative, as was the autoimmune screening. Titres for both *T. gondii* (IgG: 1677 IU/mL) and *B. hensalae* (IgG: 1:128) were elevated. Humphrey visual field showed caecocentral scotoma in the left eye. Computed tomography showed optic nerve enlargement in the left eye. Patient was diagnosed to have left neuroretinitis secondary to dual infection with *Toxoplasmosis sp* and *Bartonellosis sp*.

She was treated with oral azithromycin 500 mg once a day for 4 weeks and intravenous methylprednisolone 250 mg 4 times a day for 3 days, followed by oral prednisolone in tapering dose over 4 weeks. Her left visual acuity improved to 6/12 with resolution of the clinical signs (Figs. 3 and 4).

Discussion

Toxoplasma gondii and *Bartonella hensalae* may rarely coexist in a feline, causing dual infection. Close proximity with an infected feral cat is the main risk factor. A study done in Iraq among 207 stray cats showed that 30% are positive for *T. gondii*, while 15% are positive for *B. hensalae*, and 6.3% harbour both organisms.[2] In 2011, a local study established that DNA of *B. hensalae* was identified in 11.5% of fleas, which act as vectors for infection.[3]

Typical CSD presentation is fever, headache, anorexia, nausea, vomiting, and regional lymphadenopathy. In 25% to 60% of patients, there is papular or pustular rash at the inoculation site. The prevalence of ocular bartonellosis in CSD is 5-10%, with neuroretinitis as the most common ocular manifestation.[4] Other presentations include Parinaud's oculoglandular syndrome and uveitis. In neuroretinitis, a macular star may develop only after one to two weeks of the initial presentation. These typical presentations of CSD were absent in this patient.

The pathophysiology of macular oedema in neuroretinitis is increased permeability of disc vasculature, with fluid exudate into the peripapillary area. Involvement of the papillomacular bundle results in ceococentral scotoma, as in our patient. Non-arteritic ischaemic optic neuropathy was a possible differential diagnosis

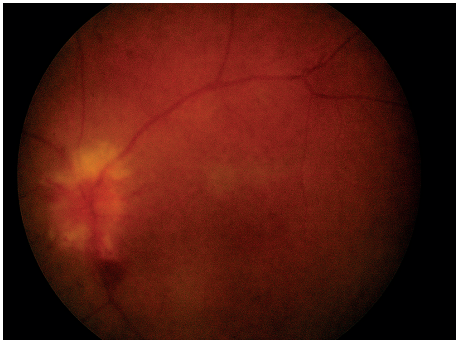

Fig. 1. Left eye fundus photo showing optic disc swelling with inferior disc haemorrhage.

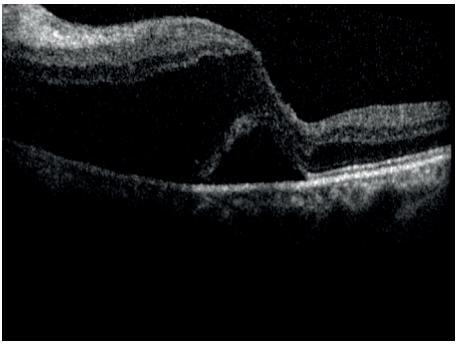

Fig. 2. Left eye OCT showing macular oedema in the papillomacular area at presentation.

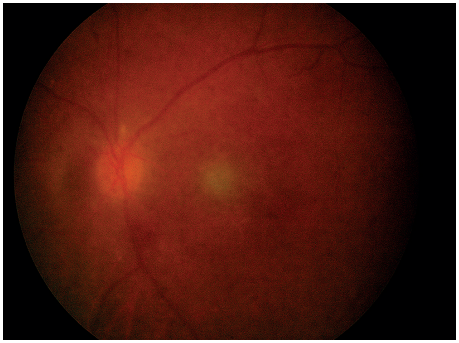

Fig. 3. Left eye fundus photo showing well-defined optic disc with resolution of inferior disc margin.

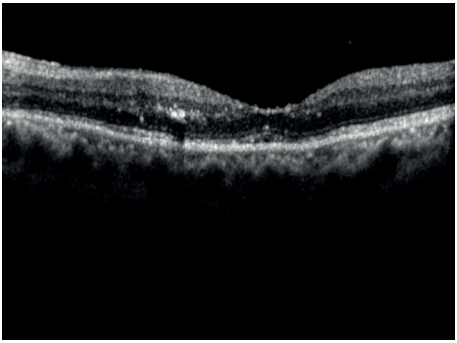

Fig. 4. Left eye OCT showing resolved macular oedema upon completed treatment.

based on the patient's age and comorbidities. However, the sudden onset of blurred vision and pain on eye movement were more suggestive of optic nerve inflammation, as was confirmed by serology.

Antibiotics form the mainstay of treatment. Azithromycin is preferred due to its ability to be concentrated in phagocytic cells, which enhances its efficacy, especially against intracellular pathogens like *T. gondii* and *B. hensalae*.[5] Both ocular toxoplasmosis and bartonellosis have good visual prognosis with treatment. Huang *et al.* reported in 2017 that final visual acuity of 20/40 or better was achieved in 74% of patient with ocular toxoplasmosis.[6] Tan *et al.* reported that 76.9% of patients with ocular bartonellosis in Malaysia had a final visual outcome of 6/18 or better.[7] From our literature search, most reported cases were single infections either by *T. gondii* or *B. hensalae*. We could not find concurrent dual organisms *T. gondii* and *B. hensalae* causing neuroretinitis being reported.

Conclusion

Toxoplasmosis gondii and *Bartonella hensalae* may cause co-infection in endemic areas. The identification of causative organisms will facilitate the management and provide better outcomes.

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