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## Expert Opinion

### INNOVATION IN MEDICAL EDUCATION: MIND MAPPING IN PSYCHIATRIC PRACTICE

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#### ABSTRACT

Mind mapping is a technique and thinking tool that can be utilized in psychiatry to improve history-taking, documentation, and management of the case. The objective of this paper is to innovate history-taking and documentation format and help to improve productivity in teaching and learning of psychiatry. The 'why' and 'how' are described and illustrated to give the example of the practicality aspect of mind maps in psychiatric practice. Since the individual mind is working independently, freedom of choice is tolerated when drafting the mind maps.

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#### INTRODUCTION

Mind Mapping is a technique and a thinking tool that can be used for comprehensive note-taking and documentation. It embraced visual and graphic thinking tools that can be harnessed for multiple thinking and memorizing activities. The process of creating a mind maps employ the entire range of cognitive skills which involve both right and left hemisphere of the brain simultaneously [1].

The advantages of using mind maps include

- (a) it defines the idea in a clearer picture.
- (b) help us to focus on the issue than its ramifications.
- (c) it helps one to see the holistic picture of the issues and their ramifications.
- (d) it shows association and hierarchy of importance between pieces of information and the rests.
- (e) chooses of keywords are made loose, flexible, and independent to allow association of ideas as well as
- (f) enhance memory as it uses total brain thinking.

This paper tries to innovate the history-taking format in psychiatry utilizing the brain mapping process to leverage the creativity aspect in improving memory of the case, improve documentation, and steadfast clerking and documenting process.

In the end, it will help to improve the productivity of teaching and learning relevant to the new era of

imparting neuroscience knowledge to education and all aspect of life.

#### THE NEED

Mind Map for psychiatric usage is modified based on the format of history-taking and mental status examination that generally has been accepted and needs to be adhered to, universally.

Psychiatrists who used to lend their ears after hearing the presentation of cases one after another are often overburdened with multiple stories in history-taking that often overwhelming their minds resulting in mental fatigue and exhaustion. Their mind needs to classify the information, register, restore and retrieve them so that whenever they are required, they can be readily available.

Psychiatric lecturers and examiners are trainers who teach and examine medical students in medical schools. They need to evaluate the completeness of history-taking, physical and mental status examination and evaluate the differential diagnosis before giving marks to students. They may need to examine several students each day and the process requires many hours of fair and square assessment followed by keeping the record for documentation purposes.

To manage cases, psychiatrists require a summary

of cases. A holistic summary in a single page gives a holistic look at the case and comprehensive management can be laid down.

Students can use this technique to steadfast history-taking, documenting it, and end up with a smooth presentation.

## THE WRITING

The identification data should be written in the upper-middle center of the page. This image creates a downward branch to the center to denote the flow of information from identification data to the chief complaint.

From the chief complaint, the next stage is to draw the downward branches of the past psychiatric history followed by the past medical/surgical illness to the family history, personal history, social, drug and allergic and finally to the personality trait of the patient. Bear in mind, that by going downward, space will be occupied by too many topics and the flowery branches will not be seen.

To leverage the space on the right and the left, it is suggested that the history should be put to the right and the MSE is put on the left side. This will reflect the 'mirror image' of symptoms and signs so that the psychiatrist can judge the synchronicity between elicited symptoms and observable signs. The synchronicity between symptom and signs give added advantage for the formation of differential diagnoses and a provisional diagnosis.

The notes should be written as concisely as possible to leverage the space. Space austerity is the key element in mind maps. Modification is allowed according to the thought flow of the practitioner.

In some cases, to the contrary, the psychiatrist may want to start with a diagnosis first especially when his documentation comes after the case had been fully presented. The subsequent branches may include the chronology of the case or the elaboration of the first symptoms and the subsequent branches may follow similar trends of narrative pursuit.

## THE CONTENT

In the usual brain mapping exercises, central to the picture is the principal idea or the principle themes of the presentation. From the central image, branches are created so as it flows out in a curve. On these branches, the key concept is placed and labeled according to keywords. The first-order branches divaricate into the second-order branches, radiate out to the third-order branches extending the idea organically and naturally [2].

In the psychiatric mind-mapping exercise, the content would consist of the psychiatric history-taking format include the Mental Status Examination (MSE), investigation, and management. To complete the formulation of the case, the predisposing factors, precipitating factors, and the perpetuating factors

need to be identified and recorded accordingly (Figure 1).

The keywords chosen should be made loose, flexible, and independent (unbounded to one inflexible specific signs or symptoms) to generate a flexible association of probable diagnoses. This is especially true in the case of diagnosis generation in the cross-discipline area of specialization like neurology and psychiatry. For instance, an epileptic attack which begins with an olfactory aura or gustatory aura which lead to automatic movement of chewing and smacking of the lip is known as an uncinat epileptic attack (in neurology) [3] but similar automatic movement due to the adverse effect of antipsychotics in psychiatry are known as Tardive dyskinesia [4]. Therefore, before a definite cause is made known, it is better not to be too specific in choosing the keyword.

## DISCUSSION

It is impracticable to debate whether this technique is a true mind map or a pseudo mind map. To my mind, it must have slightly deviated from Buzan's mind map because there is already a generally accepted psychiatric history-taking format to which one needs to adhere to.

Nevertheless, mind maps help to improve memory signify through the beautiful and colorful images, enhance thinking processes by finding the synchronicity between 'mirror image' of the sign and symptom that will help in making the differential, provisional, and the final diagnoses (Figure 2).

Notwithstanding, it is imperative to understand that the individual brain is working independently from person to person. Therefore, there shouldn't be any stringent rule on 'how and what' to draw and draft (Figure 3).

## CONCLUSION

In the nutshell, mind mapping is usable, practical, and user-friendly to be used in the psychiatric setting.

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# MIND MAPPING IN PSYCHIATRIC PRACTICE



Figure 1: Psychiatric mind-mapping exercise.



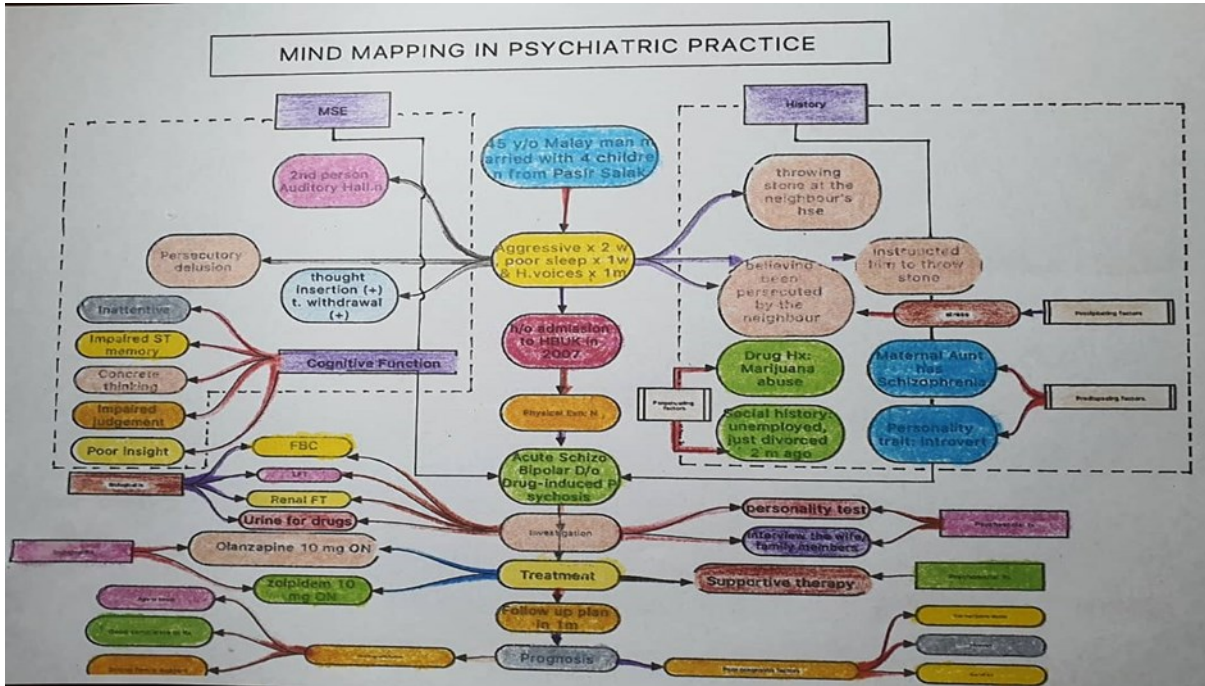


Figure 2: Mind mapping in Psychiatric practice.

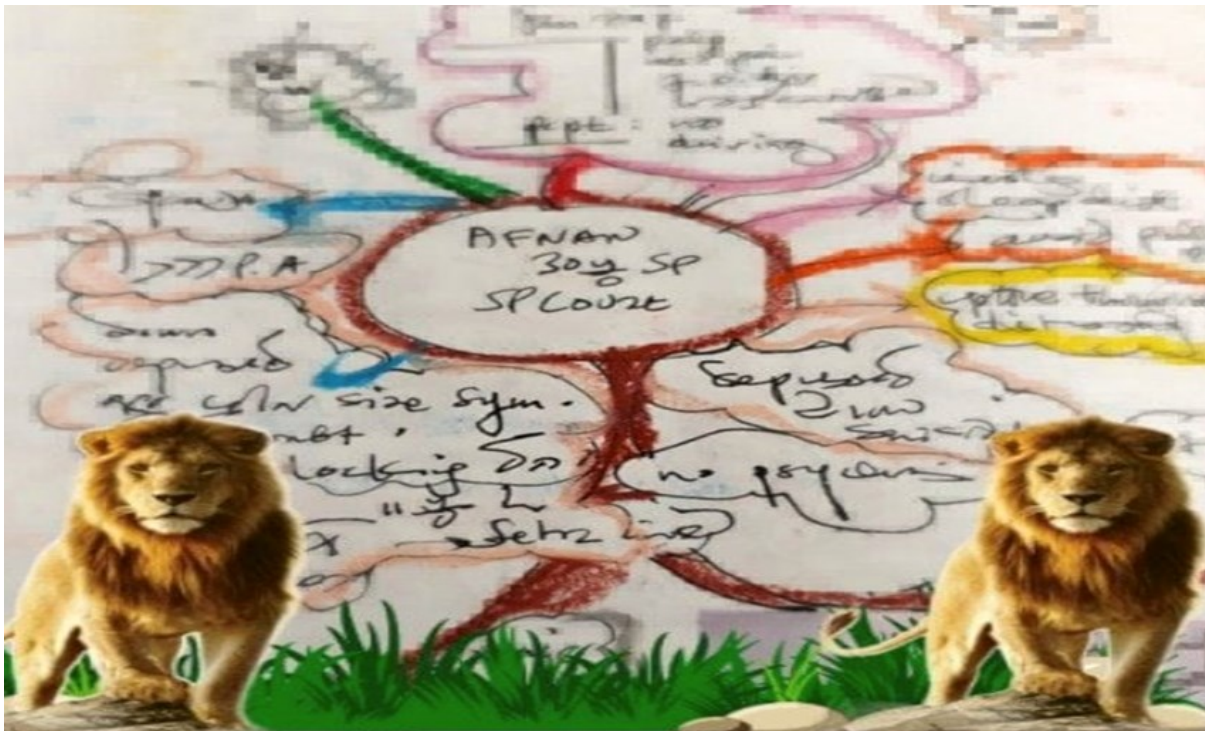


Figure 3: No rule on 'how and what' to draw and draft mind map.

Original Article

A 5-YEAR RETROSPECTIVE REVIEW OF CORNEAL ULCERS IN NORTHERN MALAYSIA

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ABSTRACT

Corneal ulcer is a common ocular infection which may result in devastating visual impairment and significant morbidity. In view of the paucity of local corneal ulcer data, we aim to evaluate the predisposing factors, disease patterns and clinical outcomes of corneal ulcer in northern Malaysia. A retrospective review of medical and microbiological records of all patients treated for corneal ulcer from 2015 to 2019 at Hospital Sultanah Bahiyah was performed. Socio-demography, predisposing factors, clinical characteristics, causative organisms and final visual outcome were analysed. A total of 408 patients were treated as corneal ulcer during our study period. The most common predisposing factor was ocular trauma (n=212, 52.0%), followed by contact lens-related (n=47, 11.5%), bullous keratopathy (n=30, 7.4%), corneal-suture related (n=25, 6.1%), ocular surface disease (n=21, 5.1%), eyelid pathology (n=14, 3.4%), exposure keratopathy (n=13, 3.2%) and pre-existing cornea dystrophy or degeneration (n=11, 2.7%). Positive yield from corneal scrapping was acquired in 213 eyes (52.2%). The commonest bacteria isolated was *Pseudomonas* sp. (85, 20.8%) while fungal growth contributed to 9.6% of cases. Corneal ulcer size of more than 4mm (p<0.001), centrally located ulcer (p<0.001) and presence of hypopyon (p<0.001) were significantly related to worse final visual acuity. Majority (n=364, 89.22%) of the patients healed while 16 (3.9%) patients required penetrating keratoplasty, 16 (3.9%) underwent evisceration and 12 (2.9%) was treated with glue and bandage contact lens. In conclusion, ocular trauma and contact lens were the commonest cause for corneal ulcer in this study. *Pseudomonas* sp was the commonest bacteria isolated. By understanding the local statistics, preventive measures can be identified and prompt intensive treatment can be initiated to reduce the morbidity related to corneal ulcer and improve visual outcome.

INTRODUCTION

Corneal ulcer is a leading cause of preventable corneal blindness. It is estimated that 1.5 to 2 million corneal ulcer cases resulted in unilateral blindness annually worldwide [1]. In developing countries, limited access to health care services and lack of eye-care awareness were the major obstacles to early medical treatment. This subsequently led to higher morbidity, increased disease burden, longer duration of treatment and hospitalization, and surgical intervention. Predisposing factors and causative organisms of corneal ulcer varies between developed and developing countries, with bacterial infection being the predominant causative organism in developed countries compared to fungal infection in developing countries [1].

Based on the largest single-centre study on corneal ulcer in Malaysia, contact lens was the commonest

predisposing risk factors followed by ocular trauma, with *Pseudomonas* sp being the commonest causative organisms in Malaysia [2]. There are limited studies on corneal ulcer in the northern part of Malaysia especially in the state of Kedah. This study is designed to investigate the predisposing factors, disease patterns, causative organism, and clinical outcomes of corneal ulcer in Hospital Sultanah Bahiyah, a tertiary referral centre for the northern region of Malaysia.

MATERIALS & METHODS

This is a retrospective study involving patients treated as corneal ulcer and investigated with corneal scrapping in Hospital Sultanah Bahiyah between January 2015 and December 2019. This study was approved by the Malaysian National Institute of Health and was registered in the



National Medical Research Registry (NMRR -20-1473-55317).

Data acquired via the electronic hospital information systems (EHIS) of Hospital Sultanah Bahiyah were reviewed. Data collected include patients' demographic information, referral source, onset of first symptoms prior to presentation, predisposing factors, clinical features of corneal ulcer, result of culture from corneal scraping, duration of hospitalization and final visual outcome.

Snellen visual acuity was used to evaluate the presenting and final vision and categorised into good (6/6 to 6/12), moderate (6/15 to 6/60) and severe (worse than 3/60) [2] visual acuity. The location of the ulcer was determined based on 3 zones of the cornea. The central zone is 1 to 3 mm in diameter at the center of the cornea, bordered by the paracentral zone, a 3 to 4 mm area from the margin of the central zone; and the peripheral zone which is the remaining cornea outside of the paracentral zone [3]. The corneal ulcer size was defined as the largest diameter of the cornea ulcer measured prior to corneal scraping which is divided into small (0 to 2 mm), medium (2 to 4 mm) and large (5 or more). Corneal smear was sent for gram stain and in vitro cultures on blood agar, chocolate agar, Sabouraud dextrose agar, and McConkey agar.

According to the local hospital's practice, bacterial corneal ulcers were mostly treated with intensive combined topical fortified gentamicin 0.9% and ceftazidime 5% eye drops or combined topical fortified gentamicin 0.9% and cefuroxime 5% as empirical treatment. The treatment would be revised based on clinical response and culture and

sensitivity results. Intensive topical amphotericin B 0.15% and fluconazole 2% were the empirical treatment for clinically-appearing fungal ulcer. Systemic antibiotic or antifungal were considered in limbal involvement, impending perforation, perforated ulcer, scleral extension or endophthalmitis. Surgical interventions like evisceration, penetrating keratoplasty, glue with bandage contact lens and temporary tarsorrhaphy were done when indicated.

Patients were either treated as an outpatient or admitted to the eye ward based on the clinical severity. They then underwent regular follow-ups at the eye clinic until the corneal ulcer healed and final visual outcome achieved.

SPSS 22.0 were used to analyse the data. Categorical data is presented as frequency and percentage, whereas continuous data is presented as mean and standard deviation. Pearson's chi square was used to determine the difference between categorical data. A *p* value of less than 0.05 is considered as statistically significant.

## RESULTS

There were 408 patients treated with corneal ulcer in Hospital Sultanah Bahiyah from January 2015 to December 2019. The female to male ratio was 1:2. The mean age of the patients was 49.6 years (range: 9 to 87 years). Majority of the patients were Malay (80.4%), followed by Chinese (12.5%) and Indian (2.9%), conforming to the local ethnicity distribution. Most of the patients were referred from government health clinic or emergency department of Hospital Sultanah Bahiyah (52.5%). The complete data on the socio-demographic is shown in Table 1.

Table 1: Socio-demographic data.

Sociodemographic		n (%)
Gender	Female	273 (33.1)
	Male	135 (66.9)
Age	<21	25 (6.1)
	21-40	131 (32.1)
	41-60	112 (27.5)
	61-80	124 (30.4)
	>80	16 (3.9)
Ethnicity	Malay	328 (80.4)
	Chinese	51 (12.5)
	Indian	12 (2.9)
	Foreigner	17 (4.2)
Source of referral	Emergency department/ Government health clinic	214 (52.5)
	Private health clinic	8 (2.0)
	Private ophthalmologist	71 (17.4)
	Other specialties	7 (1.7)
	Walk-in cases	78 (19.1)
	Unknown	30 (7.4)

Slightly more than half of the patients (n=229, 56.1%) sought medical attention relatively early within three days after onset of symptoms, while 179 (43.9%) patients presented after three days. A total of 153 (37.5%) patients had an ulcer size of less than 2 mm, 128 (31.4%) had ulcer size of 2 to 4 mm and 127 (31.1%) had ulcer diameter of more than 4 mm. Most corneal ulcers were located paracentrally (181, 44.4%) followed by central (140, 34.3%) and peripheral zone (87, 21.3%). Hypopyon was present in one third (60 eyes, 33%) of the study population. Slightly more than half (207, 50.7%) of the patients required hospitalization for more than seven days for optimal treatment while 63 (15.4%) patients was treated as outpatient including those who refused hospital admission. Ocular trauma was the main predisposing factor of corneal ulcer (n=212 eyes, 52%) followed by contact lens related (n=47, 11.5%), bullous keratopathy (n=30, 7.4%) and corneal suture related (n=25, 6.1%). Thirty five (8.6%) cases had no known predisposing factor. Almost half of the patients (191, 46.8%) presented with severe vision loss with visual acuity of less than 3/60. Clinical characteristics were summarised in Table 2.

There was no significant difference between the presenting intervals of initial symptoms with visual outcome in this study. Marked Improvement of vision was observed in corneal ulcers of less than 4 mm in diameter. Central location of corneal ulcers, presence of hypopyon and high intraocular pressure (IOP) (more than 21 mmHg) was significantly related to poorer visual outcomes ( $p < 0.001$ ) (Table 3). Patients with bullous keratopathy, ocular surface disease and pre-existing corneal pathology also showed lesser degree of visual improvement after treatment.

*Pseudomonas sp.* was the commonest causative bacteria isolated (20.8%), followed by *Staphylococcus aureus* (7.1%), *Streptococcus pneumonia* (4.9%), Coagulase-negative staphylococci (CoNS) (1.5%), *Bacillus sp.* (1.2%) and *Hemophilus Influenza* (1.0%). Thirty cases (9.6%) had fungal growth while no pathogen was isolated in 195 of samples (47.8%). Table 4 summarised the causative organism of corneal ulcer.

## DISCUSSIONS

In this study, male predominance was similar to other studies conducted in Indonesia and Thailand [4,5]. Studies in Malaysia found that male has higher incidence compared to female and predominantly in those aged 21 to 40 years (32.1%) [2,6]. This may be due to the fact that young males are the main work force, rendering themselves to higher risk of industrial ocular injury. Eighty per cent of corneal ulcer patients were Malays corresponding to the ethnicity composition of Kedah. [7].

We received most of our referrals from government clinics and emergency department, followed by private ophthalmology clinics. About 43.9% of patients presented later than three days. Hooi et al showed the average time to presentation was 4.7

Table 2: Clinical characteristics, complications and surgical intervention.

	n (%)
<b>Presentation interval</b>	
≤3 days	229 (56.1)
>3 days	179 (43.9)
<b>Laterality</b>	
Right eye	216 (52.9)
Left eye	192 (47.1)
<b>Size, largest diameter</b>	
≤2mm	153 (37.5)
2-4mm	128 (31.4)
>4mm	127 (31.1)
<b>Location</b>	
Central	140 (34.3)
Paracentral	181 (44.4)
Peripheral	87 (21.3)
<b>Hypopyon</b>	
Present	60 (33.3)
Absent	120 (66.7)
<b>Hospitalization duration</b>	
≤ 7 days	138 (33.8)
> 7 days	207 (50.7)
Not admitted	63 (15.4)
<b>Predisposing risk factors</b>	
Ocular trauma	212 (52)
Contact-lens related	47 (11.5)
Unknown	35 (8.6)
Bullous keratopathy	30 (7.4)
Corneal-suture related	25 (6.1)
Ocular surface disease	21 (5.1)
Eyelid pathology	14 (3.4)
Exposure keratopathy	13 (3.2)
Pre-existing corneal opacity/ Dystrophy/ Degeneration	11 (2.7)
<b>Presenting visual acuity</b>	
Good : 6/6 – 6/12	91 (22.3)
Moderate : 6/15 – 3/60	126 (30.9)
Severe loss : < 3/60	191 (46.8)
<b>Final visual acuity</b>	
Good : 6/6 – 6/12	156 (38.2)
Moderate : 6/15 – 3/60	117 (28.7)
Severe loss : < 3/60	135 (33.1)
<b>Complication</b>	
Corneal perforation	30 (7.4%)
Exogenous endophthalmitis	19 (4.7%)
<b>Surgical intervention</b>	
Evisceration	16 (3.9%)
Penetrating keratoplasty	16 (3.9%)
Glue and bandage contact lens (BCL)	9 (2.2%)
Temporary tarsorrhaphy	3 (0.7%)

Table 3: Presenting and final visual acuity vs clinical features.

Parameters	Final visual acuity <sup>a</sup> , n (%)			p Value <sup>b</sup>
	Good	Moderate	Severe	
Presenting Interval				
≤ 3 days	94 (41.1)	63 (27.5)	72 (31.4)	0.416
> 3 days	62 (34.6)	54 (30.2)	63 (35.2)	
Size, largest diameter				
≤ 2 mm	85 (55.5)	44 (28.8)	24 (15.7)	<0.001
2-4 mm	59 (46.1)	40 (31.2)	29 (22.7)	
> 4 mm	12 (9.4)	33 (26.0)	82 (64.6)	
Location				
Central	28 (20.0)	32 (22.9)	80 (57.1)	<0.001
Paracentral	88 (48.6)	61 (33.7)	32 (17.7)	
Peripheral	40 (46.0)	24 (27.6)	23 (26.4)	
Hypopyon				
Present	45 (23.4)	51 (26.6)	96 (50.0)	<0.001
Absent	111 (51.4)	66 (30.5)	39 (18.1)	
Intraocular pressure (IOP)				
10 - 21 mm Hg	152 (45.0)	108 (32.0)	78 (23.0)	<0.001
> 21 mm Hg	4 (5.7)	9 (12.9)	57 (81.4)	
Predisposing ocular factors				
Ocular trauma	102 (48.1)	63 (29.7)	47 (22.2)	<0.001
Contact lens-related	22 (46.8)	17 (36.2)	8 (17.0)	
Bullous keratopathy	0 (0.0)	2 (6.7)	28 (93.3)	
Corneal suture-related	6 (24.0)	12 (48.0)	7 (28.0)	
Ocular surface disease	4 (19.1)	5 (23.8)	12 (57.1)	
Eyelid pathology	6 (42.9)	2 (14.2)	6 (42.9)	
Exposure keratopathy	5 (38.5)	5 (38.5)	3 (23.0)	
Pre-existing corneal Opacity/ Dystrophy/ Degeneration	0 (0.0)	3 (27.3)	8 (72.3)	
Unknown	11 (31.4)	8 (22.9)	16 (45.7)	

Table 4: Causative Organisms.

Causative organisms	n (%)
Pseudomonas spp	85 (20.8)
Staphylococcus aureus	29 (7.1)
Streptococcus pneumonia	20 (4.9)
Coagulase-negative staphylococci	6 (1.5)
Bacillus spp	5 (1.2)
Hemophilus Influenza	4 (1.0)
Fungal	30 (9.6)
Others	34 (6.1)
Unknown	195 (47.8)

**Table 5:** Presenting and final visual acuity vs clinical features.

Year	Aurthors	Study Period	Region	Patients	Risk factors (%)	Positive cultures (%)	Organisms		Microbiological profiles
							B(%)	F(%)	
Malaysia									
2017	Nazri O et al. (2)	2006-2013	Selangor	174	CL (47.2)	46.8	38.6	1.3	Pseudomonas (31.6%); S.aureus (5.7%)
2019	Yap YJ et al (6)	2015-2017	Kelantan	137	Ocular trauma (70.8)	75.9	51.1	24.8	Pseudomonas (27.1%); S.aureus (9.5%); Fusarium (9.5%)
2005	Hooi SH et al. (8)	1999-2002	Johor	100	Ocular trauma (41%)	-	39.6	-	Pseudomonas (58.8%); S.aureus (10.5%).
2008	Kursiah et al. (11)	2003-2004	Perak	28	Ocular trauma (32%)	70	64	36	Pseudomonas (30%)
Other countries									
2012	Napaporn T et al. (14)	2003-2006	Thailand	305	Ocular trauma (43.9%)	25.6	49.3	46.3	Fusarium(26.9%); Pseudomonas(14.9%)
2015	Asroruddin et al. (4)	2008-2011	Indonesia	216	Ocular trauma (45.8)	46.7	100	-	Pseudomonas (24.7%); S.epidermidis (18.4%)
2019	Weihan T et al. (10)	2012-2016	Singapore	230	CL (64.3)	100			Pseudomonas (51.7%); CoNS
2015	Lalitha et al. (13)	2002-2012	India	23897	-	59	24.7	34.3	Fusarium (14.5), Aspergillus (8.8); S.pneumoniae(7)
2019	Lin et al.(15)	2010-2018	China	7229	-	42.8	52.7	57.6	CoNS (28.6); Fusarium (23.5), Aspergillus (12.2)
2018	Khor et al. (12)	2012-2014	Asia	6626	Ocular trauma (34.7)	70.7	38	32.7	Fusarium (18.3); Pseudomonas (10.7); Aspergillus (8.3)
2017	Tan et al.(16)	2004-2015	Manchester, UK	4229	-	32.6	90.6	7.1	CoNS (24.4); S.aureus (15.1);Streptococci (13.3)
2020	Asbell et al. (17)	2009-2018	US	6091	-	100	100	0	S. aureus (35.9); CONS(29); H.influenza (13)

days in a tertiary hospital in Johor, Malasia [8]. The factors that delay patients from seeking medical help include lack of awareness, self-remedy, alternative treatment and over-the-counter medication as well as transportation problems [9]. For that, the public should be educated regarding the risk factors and severity of corneal ulcers and importance of early medical attention.

Predisposing factors vary in different populations. Our study found ocular trauma to be the most common predisposing risk factor (52.0%) followed by contact lens use (11.2%). Yap et al. showed ocular trauma (70.8%) was the main risk factors of corneal ulcer in East coast, Malaysia as well, where primarily agriculture activities was predominant, resembling the socioeconomic background of our study location [6]. In a similar sociodemographic background in central part of Thailand where agriculture is the main source of income, Saratorn et al found that ocular trauma (47.8%) was the commonest risk factors for corneal ulcer [10]. Nazri et al. reported that contact lens-related corneal ulcers tend to be more in the urban area (59.2%) as contact-lens are more readily available and used [2]. Contact lens were the commonest predisposing factors in Singapore (64.4%), followed by ocular

trauma as contact lens are widely used by young females [11].

We found ulcers larger than 4 mm, central location and presence of hypopyon upon presentation resulted in a significantly ( $p < 0.001$ ) poorer final visual outcome. Although ocular trauma and contact lens usage appeared to be the main predisposing factors, the overall visual improvement after treatment were better compared to those with underlying ocular pathologies and pre-existing poor visual. Weihan T et al reported that poorer visual outcome was associated with older age, non-contact lens wearer, larger corneal ulcers and trauma [11].

A total of 213 (52.2%) corneal scrapping samples yielded positive cultures. This culture yield is slightly low compared to findings by Yap et al in Kelantan (75.9%) and Kursiah et al in Perak (70%) [6,11]. Local studies in different states in Malaysia also recorded *Pseudomonas sp* as the commonest causative organism, [2,6,8,12] agreeing with studies from Singapore and Indonesia [4,11]. These can be explained by similar geographical and socioeconomic characteristics in these locations. *Fusarium sp* was found to be the main

causative organism in Asia particularly Thailand and India [13,14,15]. Coagulase-negative staphylococci (CoNs) was more common in China and United Kingdom (UK) while studies from the United States revealed *Staphylococcus aureus* as the main causative organism [16,17,18].

Our patients were empirically treated with combined topical aminoglycoside (gentamicin) and cephalosporin (ceftazidime or cefuroxime) after being clinically diagnosed as bacterial ulcers while topical amphotericin B and fluconazole were prescribed to those with presumed fungal keratitis. More specific antibiotics or antifungal were administered according to the culture and sensitivity results. Only 30 eyes (7.4%) were complicated with corneal perforation while 19 eyes (4.7%) developed exogenous endophthalmitis. Sixteen (3.9%) patients required penetrating keratoplasty and another 16 (3.9%) had to undergo evisceration.

We found 135 patients (33.1%) had final visual acuity worse than 3/60, almost similar to the results by Nazri et al, 21.9% [2]. Visual impairment has significant impact on individuals and society. It is important to raise public awareness regarding the risk factors of corneal ulcer, the preventive measures especially in high-risk occupation, and the urgency to seek treatment to achieve better visual outcome.

Being a retrospective design, this study has limited more thorough correlation to be established with regards to specific demographic features such as occupation, education level, financial status, smoking status, comorbidities and disease control. Duration of treatment and hospitalisation was not analysed in view of multiple confounding factors such as patient's compliance and refusal for hospital admission.

## CONCLUSIONS

Ocular trauma was the main predisposing factor in our cohort of corneal ulcer patients and *Pseudomonas* sp was the commonest causative organism. Large corneal ulcer, central ulcer location, presence of hypopyon and underlying ocular pathologies contributed to worse visual outcome. The awareness of eye disease and prevention need to be emphasize in community health promotion. Routine ophthalmology training programme for primary healthcare practitioners is indeed crucial for early referral and definitive treatment in order to achieve better visual outcome.

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Original Article

VISUAL OUTCOME OF PARS PLANA VITRECTOMY FOR DROPPED NUCLEUS FOLLOWING COMPLICATED PHACOEMULSIFICATION

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ABSTRACT

*Phacoemulsification complicated with dropped nucleus requires pars plana vitrectomy for removal of the dropped lens fragments. Many factors determined the visual outcome. The objective of this study was to evaluate the visual outcome and complications following pars plana vitrectomy for dropped nucleus post complicated phacoemulsification. This study was a retrospective, non-comparative interventional case series. A total of 90 patients were reviewed. Timing of surgery, intraocular lens implanted, size of dropped lens fragments and complication(s) were analyzed against visual outcome. The results revealed that 62.2% had visual acuity of  $\geq 6/12$ . Better visual outcome was associated with delayed vitrectomy and more than a quarter dropped nucleus size. Types of intraocular lens implanted did not affect visual outcome. Complications included high astigmatism (10%), epiretinal membrane (7.8%), rhegmatogenous retinal detachment (5.6%), choroidal detachment (5.6%), and cystoid macula oedema (3.3%). In conclusion, vitrectomy within six to eight days and larger dropped nucleus fragment size were associated with better visual outcome.*

INTRODUCTION

In 2002, only 39.7% of cataracts in Malaysia were managed by phacoemulsification technique while most were operated with extracapsular cataract extraction [1]. The rate of phacoemulsification continued to rise to 87.4% in 2014 [2]. With increasing number of phacoemulsifications performed, the rate and incidence of complications such as posterior capsular tear and dropped nucleus have shown corresponding increment, especially during the early learning curve of surgeons. Dropped nuclear fragments require removal of the lens fragments via vitrectomy. For more than a decade, Selayang Hospital Eye Department has been one of the national referral centres for vitreoretinal subspecialty in Malaysia, receiving cases that require vitreoretinal surgical intervention. This includes cases of dropped nucleus post complicated phacoemulsification. Dropped nucleus, or dislocation of the entire nucleus or nuclear fragments into the vitreous cavity is one of the known complications of phacoemulsification. Its occurrence is contributed by multiple factors such as polar cataract, brunescant cataract, previous vitrectomised eye, high myopia and pseudoexfoliation syndrome. Left untreated, retained lens fragments can lead to severe intraocular inflammation, cornea oedema, cystoid

macular oedema, secondary glaucoma and retinal detachment, resulting in a decrease in visual acuity [3].

This study aims to determine the visual outcome of patients who underwent pars plana vitrectomy for dropped nucleus after phacoemulsification. Timing of vitrectomy, type of intraocular lens, size of dropped lens fragments and complications were evaluated and analyzed against visual outcome.

MATERIAL & METHOD

This is a retrospective and non-comparative interventional case series. Electronic medical records of all patients who underwent pars plana vitrectomy with lens fragment removal in Eye Clinic, Selayang Hospital were retrospectively reviewed over a 3-year period between January 2015 and December 2017, which includes a total of 90 eyes from 90 patients. All the patients underwent pars plana vitrectomy with lens fragments removal. Data collected include demographic data (age and gender), laterality of involved eye, date of initial

surgery and vitrectomy, types of intraocular lens implanted, pre-existing ocular problem, category of surgeons (vitreoretinal consultant or fellow), final visual acuity and complications (intra and post-vitrectomy). The number and size of dislocated nuclear fragments, the timing of intervention, the type of intraocular lens (IOL) implanted, complications and visual outcome were analyzed. A minimum of 3 months of follow-up data after vitrectomy was necessary for inclusion in the study. Patients with pre-existing ocular disease other than cataract which could have affected the visual acuity prior to cataract surgery such as retina or macular disease, patients in whom primary aim of cataract surgery was not to improve vision such as patients with traumatic lens dislocation and uveitic cataract, defaulters or incomplete documentation were excluded.

All surgeries were performed by consultants and vitreoretinal fellows. The cases were referred either from government or private ophthalmology centers. Initial assessment was made during patient's first clinic visit. Those with high intraocular pressure (IOP) (defined as IOP of 25 mmHg or more) and oedematous cornea were managed medically (with topical antiglaucoma and corticosteroid) before being listed for operation.

All patients underwent pars plana vitrectomy under retrobulbar or general anaesthesia. Standard three-port 23G pars plana vitrectomy ports were inserted and complete vitrectomy performed via standard manner. Posterior vitreous detachment was induced if necessary with aspiration and triamcinolone staining. When possible, small nucleus fragment of less than a quarter nucleus size and cortical matter were removed using vitreous cutter. Larger pieces of nucleus fragments were removed using a 20G phacofragmentation technique through a scleral incision made with MVR blade. Vitrectomy was completed with

internal search for iatrogenic breaks. Finally, sulcus or anterior chamber intraocular lenses were implanted depending on adequacy of capsular support.

Post-operatively, patients were prescribed with topical dexamethasone and chloramphenicol every two hours for the first week and tapered off subsequently over one month. Intraocular pressure of 25 mmHg or more was treated with anti-glaucoma accordingly. Visual acuity was taken at every review until at least 3 months post vitrectomy using Snellen chart. Pearson chi-square test was performed to determine any significant difference between i) the timing of vitrectomy and visual acuity, ii) the different types of implanted IOLs and visual acuity, and iii) the size of dropped lens fragments and visual acuity and iv) any intraoperative or postoperative complications and visual acuity. A p value of 0.05 was taken as statistically significant difference between groups.

## RESULTS

### Demographic data

Of 145 patients (145 eyes) who underwent vitrectomy for dropped nucleus or dropped nuclear fragments at our centre during the period of study, 90 subjects [90 eyes] met the inclusion criteria and were included in this retrospective case review.

The mean age of patients was 65 (ranged 34 – 84) years. There was an equal gender distribution of 45 males and 45 females. Fifty patients (55.5%) had dropped nucleus fragments involving right eye and 40 patients (44.4%) had involvement in the left eye (Table 1).

### Visual acuity

At three months post vitrectomy, 62.2% (56 patients) gained visual acuity of 6/12 or better while

Table 1: Demographic data of patients.

Demography	Number of patients (n=90)
Gender	
Male	45
Female	45
Eye operated	
Right eye	50
Left eye	40
Age (years)	
Range	34-84
Mean	65

37.8% (34 patients) had visual acuity of 6/18 or worse. Seven patients (7.8%) achieved visual acuity of 6/6 and 11 patients (12.2%) had visual acuity of 6/60 or worse at three months' review.

Reasons for poor visual outcome (6/60 or worse) were due to complication[s] in eight eyes; namely rhegmatogenous retinal detachment (two eyes), choroidal detachment (four eyes), cornea decompensation (one eye), vitreous hemorrhage (one eye), cystoid macula oedema (one eye), post-operative endophthalmitis (one eye) and chronic anterior uveitis (one eye). Three patients had an unexplained cause of poor visual acuity.

### Timing of pars plana vitrectomy

All cases underwent three-port pars plana vitrectomy (PPV). The timing of the intervention surgery ranged between same day (within 24 hours) and 162 days

post phacoemulsification; with mean of 9.8 days. The reason for one patient to have vitrectomy performed late at day 162 post cataract surgery was due to his disagreeable for vitrectomy at initial stage. Fifty-two patients (57.8%) had vitrectomy done within five days and in 38 patients (42.2%) vitrectomy was done after five days of primary surgery.

Data analysis with Chi-Square test showed the timing of vitrectomy influenced the visual outcome. There was a significant difference in the final visual outcome when vitrectomy was performed within five days (early) or after five days (later) following the primary cataract surgery with p value=0.018 (Table 2).

Twenty-seven patients had visual acuity of 6/12 or better and 25 patients had visual acuity of worse

Table 2: Visual outcome following pars plana vitrectomy for phacoemulsification complicated with dropped lens fragments.

		Visual acuity at 3 months		Chi square test
		≥6/12	<6/12	
Interval of surgeries				
	Early (≤5 days) (n=52)	27 (51.9%)	25 (48.1%)	p=0.018
	Later (≥6 days) (n=38)	29 (76.3%)	9 (23.7%)	
	≤8 days (n=56)	37 (66.1%)	19 (33.9%)	p=0.095
	≥9 days (n=34)	28 (82.4%)	6 (17.6%)	
Type of IOL <sup>a</sup>				
	Sulcus IOL <sup>b</sup> (n=41)	29 (70.7%)	12 (29.3%)	p=0.08
	ACIOL <sup>c</sup> (n=46)	24 (52.2%)	22 (47.8%)	
	Aphakia (n=3)	3 (100%)	0 (0%)	
Size of dropped lens matter				
	≤1/4 nucleus (n=45)	23 (51.1%)	22 (48.9%)	p=0.03
	>1/4 nucleus (n=45)	33 (73.3%)	12 (26.7%)	
Surgeon				
	Consultant (n=32)	21 (65.6%)	11 (34.4%)	p=0.377
	Fellows (n=58)	32 (55.2%)	26 (44.8%)	

<sup>a</sup> intraocular lens

<sup>b</sup> sulcus intraocular lens

<sup>c</sup> anterior chamber intraocular lens

than 6/12 if vitrectomy was performed early (five days or earlier) following dropped nucleus. When the visual outcome was compared to delayed vitrectomy (day six or later), 29 patients had visual acuity of 6/12 or better and only nine patients had visual acuity worse than 6/12. There was a significant difference of the final visual outcome if the surgery was performed later compare to earlier with  $p=0.018$ . No significant difference if vitrectomy was performed after eight days following phacoemulsification with  $p=0.095$  (Table 2). Thus, from this case series, it can be concluded that later vitrectomy [day six to day eight] resulted in a better visual outcome. Table 2 shows overall visual outcome according to interval of surgeries.

#### Type of intraocular lens

Intraocular lens (IOL) was implanted in 87 patients of which 33 patients had IOL implantation during the complicated cataract surgery and 54 patients had IOL implantation performed at the end of vitrectomy. Of the 87 lens implanted, 41 eyes (45.6%) received

sulcus intraocular lens and another 46 eyes (51.1%) had anterior chamber intraocular lens implantation. Three eyes were left aphakic. One was due to the unavailability of sulcus intraocular lens during vitrectomy in which secondary sulcus intraocular lens was implanted later with final visual outcome of 6/9 at three months post vitrectomy, one had preexisting macerated and atrophic iris which was unsuitable for anterior chamber intraocular lens implantation with best corrected visual acuity of 6/9 and the other had choroidal detachment during vitrectomy which resolved subsequently with best corrected visual acuity of 6/7.5. Using Chi-Square test, it was shown that type of IOL did not influence the visual outcome significantly with  $p=0.08$  (Table 2). Table 4 shows overall visual outcome according to types of intraocular lens implanted.

#### Size of dropped lens fragments

Forty-five patients (50.0%) had less than a quadrant nuclear dropped while twenty-nine

Table 3: Visual outcome according to interval of surgeries.

Visual acuity at 3 months	Interval between phacoemulsification and vitrectomy					Total
	0-5 days	6-10 days	11-15 days	16-20 days	≥21 days	
≥ <sup>3</sup> 6/12	27	17	3	5	4	56
6/18 - 6/60	20	5	2	0	1	28
<6/60	5	0	0	0	1	6
Total	52	22	5	5	6	90

Table 4: Visual outcome according to types of intraocular lens (IOL) implanted in eyes with dropped nucleus.

Visual acuity at 3 months	Type of intraocular lens implanted			Total
	Sulcus	ACIOL	Aphakia	
≥6/12	29	24	3	56
6/18-6/60	10	18	0	28
<6/60	2	4	0	6
Total	41	46	3	90

patients (32.2%) had whole nucleus dropped during phacoemulsification. Twenty patients (22.2%) had only cortical matters dropped during phacoemulsification surgery (Table 5).

Statistical analysis using Chi-Square test showed size of dropped lens fragments significantly associated with visual outcome,  $p=0.03$  (Table 2). Visual acuity of 6/12 or better was seen in 33 eyes with more than a quarter dropped nucleus and in only 23 eyes with quarter or less dropped nucleus. Table 6 showed overall visual outcomes according to the size of dropped lens fragments.

### Visual outcomes comparing surgeons

From year 2015 until 2017, vitrectomy for removal of dropped lens fragments was performed by three vitreoretinal consultants and seven vitreoretinal fellows. Statistical analysis with Chi square found no significant difference in the visual outcomes comparing vitrectomy performed either by consultants or vitreoretinal fellows with  $p=0.377$  (Table 2).

### Complications following pars plana vitrectomy

Fifty-two eyes (57.8%) did not have any

complications following pars plana vitrectomy while 38 eyes (42.2%) had complications. Of the 38 eyes, 29 eyes had one complication and nine eyes had combinations of two complications (Table 7). Amongst the highest complications were high astigmatism (10%), epiretinal membrane (7.8%), choroidal detachment (6.7%), intra operative retinal tear (5.6%) and rhegmatogenous retinal detachment (4.4%).

Chi square test comparing the complication following pars plana vitrectomy with lens fragments removal to visual acuity proved that the visual acuity was worse than 6/12 whenever there was complication with  $p=0.000$ . Chi square test comparing complications to the timing of vitrectomy, dropped nucleus size and surgeons revealed no significant difference,  $p>0.05$  (Table 8).

In group where the whole nucleus dropped, 13 out from 29 patients had complications. Six patients had visual outcome of 6/12 or better. Of the 15 patients who had no complications, only two had visual acuity worse than 6/12.

Table 5: Size of dropped lens fragments.

Size of dropped lens fragments	Frequency	Percent
Cortical matter	20	22.2
1/4 nucleus matter or less	25	27.8
1/2 nucleus matter or less	13	14.4
3/4 nucleus matter or less	3	3.3
Whole nucleus	29	32.2
Total	90	100.0

Table 6: Visual outcome according to the size of dropped lens fragments.

Visual acuity at 3 months	Sizes of nucleus fragments					Total
	Cortical matter	≤1/4 nucleus	≤1/2 nucleus	≤3/4 nucleus	Whole nucleus	
≥6/12	13	10	9	3	21	56
<6/12-6/60	4	14	4	0	6	28
<6/60	3	1	0	0	2	6
Total	20	25	13	3	29	90



Table 7: Complications following vitrectomy for dropped lens fragments.

<b>Combinations of complications</b>									
	None	CD	VH <sup>l</sup>	Decom. Cornea <sup>m</sup>	Ref. error <sup>n</sup>	2 <sup>o</sup> glau- coma <sup>e</sup>	Sublux- IOL <sup>o</sup>	ERM <sup>c</sup>	Ret tear <sup>j</sup>
None	52								
RRD <sup>a</sup>	2	1					1		
CD <sup>b</sup>	2		2	1					
ERM <sup>c</sup>	6					1			
CMO <sup>d</sup>	2								1
2 <sup>o</sup> Glau-	1						1	1	
High	9								
Endoph <sup>g</sup>	1								
CSME <sup>h</sup>	1								
SIS <sup>i</sup>	1								
Ret. Tear <sup>j</sup>	3		1						
Chr. AU <sup>k</sup>	1								

<sup>a</sup> rhegmatogenous retinal detachment

<sup>i</sup> surgical induced scleritis

<sup>b</sup> choroidal detachment

<sup>j</sup> retinal tear

<sup>c</sup> epiretinal membrane

<sup>k</sup> chronic anterior uveitis

<sup>d</sup> cystoid macula oedema

<sup>l</sup> vitreous haemorrhage

<sup>e</sup> secondary glaucoma

<sup>m</sup> decompensated cornea

<sup>f</sup> high astigmatism

<sup>n</sup> refractive error

<sup>g</sup> endophthalmitis

<sup>o</sup> subluxated intraocular lens

<sup>h</sup> clinically significant macula oedema

Table 8: Complications comparing with timing of vitrectomy, dropped nucleus size and surgeons.

	<b>Complications</b>		<b>p value (Chi Square)</b>
	None (n=51)	Present (n=39)	
Timing of vitrectomy Early (≤5 days)	27	25	0.234
Later (≥6 days)	24	14	
Dropped nucleus size			0.832
Small (≤1/4 nucleus)	26	19	
Large (>1/4 nucleus)	25	20	
Surgeons			0.176
Consultants	20	10	
Fellows	31	29	

## DISCUSSIONS

### Demographics

Rate of dropped nucleus in Malaysia was 0.2% in 2014 [2]. From January 2015 to December 2017, there were 145 cases of dropped nucleus which were referred to the vitreoretinal unit at Selayang Hospital for pars plana vitrectomy and lens fragments removal.

Out of 145 cases, 90 patients (90 eyes) met the study criteria and were included in this retrospective case series review. In this review, the youngest patient was 34-years-old and the eldest was 84-years-old. The mean of years of those presented with dropped nucleus during phacoemulsification surgery was 65 years, similar to the mean age for cataract surgery population performed in Malaysia from previous years, which ranged from 65 to 65.9 years of age from 2010 until 2014 [1].

In this review, causes of dropped nucleus were not included due to inadequate data. The primary aim of this review is to evaluate visual outcomes based on timing of vitrectomy performed on patients with dropped nucleus following complicated phacoemulsification. Early surgery was defined as vitrectomy that was done within five days of primary phacoemulsification, while later vitrectomy was defined as vitrectomy performed on day six or later following primary phacoemulsification.

### Visual outcome

Surgical intervention with pars plana vitrectomy and removal of lens fragments is commonly required in the management of dropped nucleus post complicated cataract surgery. However in selective cases where the dropped lens fragments were small and consist of only cortical matter, patients may be treated medically with oral prednisolone and observation alone [4]. The visual outcomes of 6/12 or better in patients who had pars plana vitrectomy for dropped lens fragments varies from 45.5%-71.0% [5-9]. This present study finding is comparable to previous studies with visual acuity at three months was 6/12 or better in 62.2% (56 eyes).

The interval after complicated phacoemulsification and pars plana vitrectomy for removal of the retained lens fragments has been studied with no conclusion of the best optimal timing of the later surgery. Several studies demonstrated that there were no significant correlation between the interval of phacoemulsification and pars plana vitrectomy for dropped lens fragments removal with the final visual outcomes [5,6,8,9,11,12]. A systematic review and meta-analysis studying the effect of vitrectomy of three days or more in which 43 studies were reviewed and 27 studies were analyzed showed that it is best to avoid vitrectomy during the first week following phacoemulsification to clear off ocular congestion, inflammation and corneal oedema [10]. There were reports on associated reduced visual acuity, retinal tears, cystoid macula edema, choroidal detachment, moderate to severe inflammation where pars plana

vitrectomy was performed during the first two days after phacoemulsification producing inferior outcomes [11]. The meta-analysis suggested that the optimal timing of vitrectomy begins three to seven days after cataract surgery. The underlying reason was unclear, however it was presumed that the delay would allow recovery following cataract surgery just shortly before immunologic response became advanced.

This review demonstrated that there was a significant difference in the visual outcomes when compared to timing of pars plana vitrectomy with  $p=0.018$ . Of the 38 eyes that underwent later vitrectomy (more than five days following phacoemulsification), 29 eyes (76.3%) had visual acuity of 6/12 or better while only nine eyes (23.7%) had visual acuity worse than 6/12. There was no significant difference of the final visual acuity when vitrectomy was performed after day eight with  $p=0.095$ . This indicated that better visual acuity was gained when vitrectomy were performed later (from day six to day eight) following primary phacoemulsification.

A retained dropped nucleus incites inflammatory reaction. The severity and intensity increases according to the size of the dropped lens fragments. Vitrectomy performed within a week of dropped nucleus post complicated cataract surgery was associated with low inflammatory reaction in the vitreous compared when vitrectomy was done later on [11]. A few days is given to allow reduction of inflammation, regression of cornea oedema and better control of intraocular pressure. In this present study, four patients had vitrectomy within 24 hours following complicated phacoemulsification with three patients attaining visual acuity of 6/12 or better and only one patient had visual acuity of 6/18 due to high post-operative astigmatism. Previous studies found that vitrectomy after three weeks of dropped lens fragments were associated with poor visual outcome [11]. In the present study, of six eyes who had pars plana vitrectomy done at day 21 or later following phacoemulsification, four eyes had visual acuity of 6/12 or better. All the six eyes had dropped lens fragments of less than a quadrant of lens nucleus or smaller. One patient who had final visual acuity of 3/60 was due to choroidal detachment with cornea decompensation and another patient had visual acuity of 6/18 with secondary glaucoma following the procedure.

Few factors may have been contributed to the delay of vitrectomy in the present study. Delay of referral may be due to minimal lens fragments retained in the eye which necessitated observation and medical therapy to be taken first at initial point. Secondly it could be due to the obscuration of fundus view by cornea oedema and uncontrolled intraocular pressure. Patient who was not medically fit for surgery was optimized first prior to vitrectomy. Hence, a few patients in this study had vitrectomy done at 21 days or more post primary surgery.

Implantation of intraocular lens depends on the

stability of the anterior curvilinear capsulorrhexis and early management of dropped nucleus during phacoemulsification. Some surgeons may prefer anterior vitrectomy and removal of anterior cortical remnant allowing a better assessment of the capsule remnant and possibility of sulcus intraocular lens implantation. Others may prefer to immediately close the cornea wound and refer to vitreoretinal unit for further management. A few studies found that there were no significant difference in the visual outcomes comparing to the types of intraocular lens or the timing of intraocular lens implantation [5,8,12]. The finding of the present study is similar to previous studies, whereby there was no significant difference found in relation to the type and timing of intraocular lens implantation with the visual outcome of the patients.

Implantation of sulcus intraocular lens through preexisting corneal wound made during phacoemulsification reduces the possibility of high astigmatism due to suturing of cornea wound compared to patients with anterior chamber intraocular lens implantation which requires extension of the cornea wound. The incidence of astigmatism in this study was 10.0% (nine eyes). Four had sulcus intraocular lens implanted (three eyes during vitrectomy and one eye during phacoemulsification) and five eyes had anterior chamber intraocular lens implanted (four eyes during vitrectomy and one eye during phacoemulsification). In present study, there were no significant differences in relation to the type of intraocular lens used and the risk of poorer vision following pars plana vitrectomy with lens fragments removal ( $p=0.08$ ). Twelve patients with sulcus intraocular lens had vision worse than 6/12 compared to 22 patients who had anterior chamber intraocular lens implanted. However, early implantation of the intraocular lens may shorten the time of surgery during pars plana vitrectomy. Sulcus placement of an intraocular lens may allow faster cornea recovery compared to anterior chamber intraocular lens.

Lens fragment may be removed with phacofragmentation with or without the use of perfluorocarbon liquid. Perfluorocarbon liquid has been introduced as an intraoperative adjunct since 1982 and was used in several studies to assist removal of lens fragments during pars plana vitrectomy [13]. Perfluorocarbon liquid helps to protect the retina from thermal damage during phacofragmentation, avoid trauma to the retina from falling nucleus while doing phacofragmentation and in certain cases to float the dropped nucleus with removal of the nucleus through corneal limbal wound. Phacofragmentation is proven to be a safe and effective choice for removal of dropped nucleus [14]. In this present study, the surgeons did not use perfluorocarbon liquid for removal of lens fragments. Cortical matter and lens fragments that are smaller than a quadrant and of moderate hard in consistency were removed by using vitrectomy cutter Phacofragmentation technique was used in cases with harder and

bigger nuclear fragments of more than a quarter nucleus size.

A bigger and denser dropped nucleus was associated with poorer visual outcome compared to non-nuclear fragments [15]. This may be explained by requirement of higher power and longer duration of phacofragmentation when dealing with denser and bigger nuclear fragments. In our study, there was a significant difference observed in the relation of the dropped nucleus fragments size to the visual outcome with  $p=0.03$ . Interestingly, we have found that lens fragments of bigger than a quarter of the nucleus had better visual outcome compared to patients with nucleus dropped of a quarter or less. This reflects that phacofragmentation which was used for bigger nuclear segment (more than a quarter of nucleus) in this study did produce good visual outcome. This findings were not seen in previous study. Moisseiev et al in their study found a statistically significant difference in final visual outcome when comparison was made between nuclear and non-nuclear fragments [15]. However the difference was not statistically significant when final visual outcome was compared to the size of nuclear fragments (small or large). In our study, we divided the dropped lens fragments according to the size (less or more than a quarter nucleus size) and not between nuclear or non-nuclear types. This may explained the difference in our findings. A smaller nucleus size had a tendency to be treated medically first prior to surgical intervention. Patients would only be referred to vitreoretinal surgeon if failure to medical therapy ensued, development of high intraocular pressure or increased intraocular inflammation. Smaller size of dropped lens fragment referred to size of a quarter nucleus or less or only cortical matter found during vitrectomy. In our study, 22 out of 45 patients with smaller nucleus dropped size had vitrectomy done after day five (ranged 6-162 days) of phacoemulsification. Of the 45 eyes, 19 eyes had complications such as rhegmatogenous retinal detachment, choroidal detachment, corneal decompensation, vitreous haemorrhage, secondary glaucoma, chronic anterior uveitis, high astigmatism and chronic cystoid macula oedema. The poor final visual outcome may be contributed by the occurrence of complications in this group. Fifteen eyes (78.9%) had visual outcome of 6/18 or worse. These findings supported our data analysis which showed smaller nucleus size had poorer visual outcome ( $p=0.03$ ). This observation leads to our suggestion that all cases of dropped nucleus regardless of size should be treated surgically.

Vitrectomy performed by consultants who are considered as an experienced surgeon were compared to the vitreoretinal fellows in this study. Since there was more than one surgeon involved, comparison was made among them to reduce bias of this study. No significant difference was noted when visual outcomes or incidence of complications were compared to surgeons (vitreoretinal consultants and the vitreoretinal

fellows). The learning curve of a vitreoretinal trainee might be shortened and enhanced with good supervision and adequate surgical exposures in the training center.

### Complications

The incidence of complications in this present study were high astigmatism (10.0%), epiretinal membrane (7.8%), choroidal detachment (6.7%), retinal tear (5.6%), retinal detachment (4.4%), cystoid macula oedema and glaucoma (3.3%) each.

High astigmatism was observed in nine patients, which ranged from four to 12 diopter. Their visual acuity ranged from 6/12 to 6/36. One study reported astigmatism incidence of 12.5% which was related to limbal and sclerostomy incisions' sutures performed during removal of dropped lens fragments [16]. A 23G pars plana vitrectomy offers some benefits over the former 20G procedure due to creation of smaller sclerotomy incision size. It imposes less trauma on the conjunctiva and avoids the necessity of scleral suture due to its self-sealed nature. This helps to reduce surgical induced astigmatism [17]. In the current study, a standard three-port 23G pars plana vitrectomy was performed in all eyes. However, eyes with larger or harder nucleus fragments were removed using 20G phacofragmentome probe which required suturing for the larger scleral incision. In our study, of nine eyes with high astigmatism, six of them underwent pars plana vitrectomy with phacofragmentation to remove dropped nucleus. This would partly explained the incidence of high astigmatism in this group of patients. In the other three eyes who had no phacofragmentation done; one had pre-existing astigmatism, one had leaking of cornea wound post primary phacoemulsification requiring cornea wound resuturing and one had unexplained cause of high astigmatism. Anterior chamber intraocular lens (IOL) implantation is associated with higher risk of surgical induced astigmatism as a result of cornea surface irregularities from placement of multiple cornea sutures. In our study, only five from nine patients had ACIOL implantation while four patients had sulcus IOL implanted. Nevertheless in this study comparison made between types of IOL implanted and complications revealed no significant difference. Being a retrospective study, detailed and precise information pertaining to surgery may be missed due to lack of documentation. A prospective study design looking at the outcome of different types of IOL implanted in dropped nucleus patients would be of superior value in evaluating this.

In our study, seven patients (7.8%) developed epiretinal membrane (ERM). Ghasemi et al reported a lower incidence of 4.5% [18]. Their study excluded patient with preexisting diabetic retinopathy and one patient who developed ERM had pre-existing high intraocular pressure, proliferative vitreoretinopathy (PVR) and rhegmatogenous retinal detachment (RRD) before vitrectomy [18]. In our study, one patient had preexisting diabetic retinopathy and one had glaucoma after the first surgery. Four out of seven patients had vitrectomy performed later (day 13 to 44). Yeo et al observed that eyes receiving

vitrectomy within one week of primary phacoemulsification had significantly less ocular inflammatory activity [11]. Inflammation induced by residual lens materials in the eye was further exaggerated by vitrectomy surgery itself. This may predispose to ERM formation [19]. Though our study did not observe a significant difference between timing of vitrectomy and complications, trend of later vitrectomy contributing to ERM formation has been observed. A better study design looking into more risk factors, bigger subjects size and longer duration of follow-up would offer more valuable and meaningful information.

We observed development of choroidal detachment in six (6.7%) of our patients. Incidence of 2% to 15.8% was previously reported [16,20,21]. Choroidal detachment occurs when either serous fluid or hemorrhage occupies the potential space (suprachoroidal space) located in between the choroid and sclera. Early post-operative hypotony, choroidal detachment and scleral gap at sclerostomy incision site are frequent findings following a transconjunctival sutureless 23G vitrectomy [22]. Tarantola et al in their study has proposed that intraoperative cannula retraction during 23G pars plana vitrectomy has cause an increased in serous and hemorrhagic choroidal detachment due to diversion of infusion fluid into the suprachoroidal space following cannula retraction. The retraction was observed following a shallow angle trocar insertion which caused insufficient internal exposure of the cannula in the vitreous cavity and thus increasing the risk of inadvertent cannula retraction into the suprachoroidal space [23]. Valved cannula aid to minimize intra-operative fluid egression thus offer more stable intraocular fluidics and improved dynamic control of intraocular pressure (IOP) [24]. This together with proper sclera and cornea wound closure at the end of the surgery may help to reduce the occurrence of choroidal detachment. Being retrospective, we were unable to gather a detailed intraoperative information to relate the above possible mechanisms to the occurrence of choroidal detachment in our patients.

Of 90 eyes who had pars plana vitrectomy with lens fragments removal, five developed retinal tear and four had retinal detachment. Al-Khaier et.al observed higher occurrence of retinal tear and retinal detachment in eyes with ultrasound phacofragmentation usage [21]. Borne et al, who made similar observation postulated that the suction created by the large-bore ultrasound fragmentation probe may cause inadvertent engagement and traction on residual peripheral vitreous gel, causing a retinal tear and, ultimately, a retinal detachment [25]. In the current study, phacofragmentation was performed in all five patients with retinal tear and in three out of four patients (75%) with retinal detachment. The incidence of retinal detachment for this study (4.4%) was comparable to other studies that ranged from 4.1%-21.5% [6,21,26,27]. Only one

out of five eyes had good final visual acuity of 6/9, with the remaining eyes had visual acuity of worse than 6/12. Retinal detachment is one of the most common reported complication in a post vitrectomised eye following dropped nucleus. Effort and strategy should be channeled to prevent this potentially visual threatening condition. Morris et al. observed a 6-fold reduction in incidence of retinal detachment when prophylactic 360-degree laser retinopexy was performed in all patients underwent pars plana vitrectomy for removal of retained lens fragments(28). Thorough search for iatrogenic break is also a crucial element to prevent this complication.

Glaucoma is a known complication of pars plana vitrectomy ranges from 15.8%-25.53% [6,9,15]. Later vitrectomy of more than a week is associated with persistently higher intraocular pressure and poorer visual outcomes [11,21]. In this present study only two patients (2.2%) had high intraocular pressure during follow up which required anti-glaucoma treatment. Both had anterior chamber intraocular lens implanted. One patient had vitrectomy done within four days following phacoemulsification with whole nucleus dropped and the other had vitrectomy done after 83 days following dropped nucleus consisting of only cortical lens fragments.

The incidence of cystoid macula oedema increases with the longer interval of surgeries [8]. Major visual decrease was observed within the first six months up to years following vitrectomy [9]. However, in this study only three out of 90 patients were documented to have cystoid macula oedema at three months post vitrectomy. We were unable to correlate it with the interval of surgeries due to the limited sample identified. Two patients had vitrectomy done three days after phacoemulsification surgery and one patient had vitrectomy performed on the same day of primary surgery. It should also be noted that cystoid macula oedema may occur several months after surgery, thus longer study follow-up may be of more value in this study [29].

#### **Limitation of the study**

The main limitation of our study was being retrospective in nature, imposed restrictions to our data availability and adequacy. There were also several factors that may have confounded our study outcome. Variability in patient's underlying ocular conditions such as myopia, axial length differences and pre-existing retinopathy impose bias in interpretation of our results. There was more than one surgeon involved in patients' care thus this may result in variability in clinical judgement, assessment and reporting as well as surgical technique and outcome. There was also dissimilarity in the surgical instruments utilized. Tracing medical records from other referring hospitals were also challenging as most of the centers used manual data keeping. As a referral center, most patients were sent back to their respective referring hospital after vitrectomy was

done. Review of patients were done from several hospitals which may have limited resources such as unavailability of Optical Coherence Tomography (OCT) machine to document subtle underlying macula problem such as mild cystoid macula edema which could explain the cause of reduce vision. In our center, pars plana vitrectomy with phacofragmentation alone (without perfluorocarbon liquid) was opted to remove harder or bigger nucleus. While aid of perfluorocarbon liquid (PFCL) was considered the safest and most efficient way of delivering very hard nucleus or bigger nucleus fragment,28 our data suggested that in experienced hand and timely surgery, good visual outcome may still be attainable when this ideal approach may be source limited in some centers.

#### **CONCLUSION**

Our study found that in patients with dropped nucleus post complicated phacoemulsification, later pars plana vitrectomy which was performed between six and eight days carried better visual outcome. High astigmatism accounted for the highest complications followed by epiretinal membrane formation, choroidal detachment, retinal tear and rhegmatogenous retinal detachment. In the current study, we have also found that nucleus dropped of more than a quarter size showed better visual outcome when compared to smaller size of nucleus. Smaller size of dropped lens fragments tend to be treated medically first and this resulted in delayed vitreoretinal intervention and higher rates of vision threatening complications. We propose that all cases of dropped nucleus should be treated surgically regardless of its size.

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#### **DECLARATION OF CONFLICT OF INTEREST**

The authors report no conflicts of interest.

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Original Article

KNOWLEDGE, ATTITUDES AND PRACTICES TOWARDS COVID-19 AMONG PUBLIC IN MALAYSIA

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ABSTRACT

The Government of Malaysia have set and implemented various Standard Operating Procedures (SOP) as an effort to mitigate the outbreak of Coronavirus disease 2019 (COVID-19). Compliance and cooperation of Malaysian towards SOP are an indicator of the effectiveness of these mitigation measures. The aim of this research was to study the knowledge, attitudes and practices towards COVID-19 among public in Malaysia. A cross-sectional online survey of 419 Malaysian residents was conducted between 1<sup>st</sup> May 2021 to 10<sup>th</sup> June 2021. The survey instrument consisted of demographic characteristics, 11 items on knowledge, 10 items on attitudes and 9 items on practices. Descriptive statistics, chi-square tests, t-tests and one-way analysis of variance (ANOVA) were used to analyse the data obtained. The overall correct rate of the knowledge questionnaire was 84.5%. Most of participants (97.4%) knew that there currently is no effective cure for COVID-19, but early, symptomatic and supportive treatment could help most patients recover from infection and mortality rate of COVID-19. Most of participants have positive attitudes toward COVID-19 (57.5%). 96.2% of participants also agreed that events (e.g: feast, birthday party) were not encouraged to be held during pandemic COVID-19 outbreak. Most of participants (79.4%) have better practice toward COVID-19. 99.0% of participants wore mask when they go out. 98.6% of participants encouraged their family/friends to comply the current SOP. In conclusion, the study findings suggested that most of Malaysian have a good knowledge and moderate attitudes with good practices in reacting to COVID-19 outbreak.

INTRODUCTION

Coronavirus disease (COVID-19) is defined as an illness caused by a novel coronavirus, now known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2; formerly known as 2019-nCoV) [1]. The novel coronavirus was firstly recognized in December 2019, in Wuhan, China and has rapidly spread around the globe with a high contagious rate [2]. COVID-19 is considered a global public health threat and has evolved to become a pandemic crisis around the world since it causes serious complications and numerous deaths. Besides, COVID-19 can be transmitted easily via respiratory droplets and direct or indirect contact with the mucous membranes of the nose, mouth and eyes of one person to another [3]. COVID-19 patients can be asymptomatic or progress respiratory infection with main clinical symptoms like dry cough, fever, fatigue and in more severe cases, difficulty in breathing. When severe symptoms arise, immediate medical treatments are needed [4].

On January 30<sup>th</sup> 2020, World Health Organization (WHO) declared the COVID-19 outbreak as a global health emergency (World Health Organization) [5] and constituted Public Health Emergency of International Concern (PHEIC) to call for all countries to take

immediate and serious action against the spread of the virus [6]. In Malaysia, the first positive case involving three Chinese citizens was confirmed on 25<sup>th</sup> January 2020. They had entered Malaysia via Johor from Singapore on 23<sup>th</sup> January. Infection rates remained low however precautionary measures had already begun to be taken [7]. For example, the Ministry of Health (MOH) planned to have thermal scanners at every country entry points. As time passed by, the number of positive cases increased which drove the Malaysian government to make a drastic movement and action. Thus, starting on 18<sup>th</sup> March 2020, the government enforced a Movement Control Order (MCO) [7] as a means of preventing community spread since the virus can be transmitted as rapid human-to-human transmission. The MCO limited most non-essential activities outside of the home. Malaysians were only allowed to leave the house for essential activities like grocery shopping and medical treatment. Malaysians were also barred from leaving the country, as were all foreigners from entry. Non-essential industries were told to shut down or allow staff to work from home. The enforcement of MCO has significantly affected the economic activities, education, manufacturing sector, tourism industry and so on. Malaysia had not

previously experienced such an epidemic thus it was clear that society and healthcare systems are not readily prepared for COVID-19. With the scarcity of clinical measures at that time, the involvement of all parties was essential. Tagline #stayhome actively spread through mass media to encourage the public to stay at home if there is no important matter outside. Production of personal protective equipments for frontliners has been intensified by many factories. Numerous organizations held fund-raising events in order to provide medical supplies to hospitals. A temporary hospital was set up and collaborations with healthcare service providers were permitted, while additional laboratories were assigned to strengthen the capabilities of the ministry of health (MOH).

Implementation of public health protocols such as lockdown procedures, social distancing, scanning MySejahtera QR code, hand washing and wearing a mask as an immigrated efforts to flatten the rising graph of positive COVID-19 cases has caused confusion and massive fear among the society [7]. Malaysians reacted with panic and perplexity when the initial announcement of MCO was made. It leads to panic buying and people crowded public transportation hubs to go back to their hometown. It can potentially increase the risk of virus spreading and infection to other parts of the country. Due to the virus's obscurity, there has been a lot of misinformation and misunderstanding regarding the virus, like how it spreads, and the steps that should be taken to avoid infection. With a large amount of misinformation and deception published on social media, people's comprehension of COVID-19 is becoming increasingly muddled. It eventually raises concerns about Malaysians' understanding and attitudes towards COVID-19. Despite all measures taken in combating the outbreak, the public's behaviour is the one to determine whether these measures succeed or fail. Specifically, public adherence to the established preventive measures is crucial to stop the spreading of the virus. Previous research and lessons learned from global outbreaks suggested that knowledge and attitudes concerning contagious disease are tied to public sentiment, which can further complicate efforts to curb the disease's spread [8].

Citizen's devotion has been linked to their knowledge, attitudes and practices (KAP) towards COVID-19. KAP is an important primary key in public health regarding health prevention and promotion [9]. It plays a vital role in determining society's willingness and acceptance to practice behavioural change measures set by health authorities. In order to ease the controlling of pandemic COVID-19 in Malaysia, it is highly reliant on everyone's understanding of the virus, cooperation and compliance. KAP studies will give baseline information for determining the type of intervention needed to alter people's misconceptions of the virus [7]. Assessing KAP of COVID-19 among the public will promote better insight and give the right knowledge regarding COVID-19 to ensure suitable interventions and preventions are taken. In this research project, we are mainly focused on conducting a survey to investigate the KAP towards COVID-19 among the

public in Malaysia to implement effective public health interventions.

## **METHODS**

### **Study design**

The study was conducted during MCO 2.0 which started from 1<sup>st</sup> May 2021 until 10<sup>th</sup> June 2021. A quantitative approach was utilised to achieve the objectives of this study. A cross-sectional survey was appropriate to conduct for collecting the information about COVID-19 in Malaysian context. Social media was used to call for participation.

### **Sampling**

The target sample size was at least 385 respondents, determined by identifying the smallest acceptable size of a demographic subgroup with a  $\pm 5\%$  of margin error and 95% of confidential level [10]. The researchers opted to use Google form as an online survey since it is not feasible to conduct a systematic nationwide sampling during this period. Malaysian citizens above the age of 18 and recently residing in the country were eligible to participate in the survey. Several strategies were used to reach as many respondents as possible in Malaysia within 40 days data collection period. Social media (Facebook and Instagram), WhatsApp and Telegram were the platforms used to disseminate this questionnaire. WhatsApp and Facebook were chosen since they were the most popular social and communication platforms nowadays. Instagram are renowned among the younger generations while older Malaysians generally preferred Facebook.

As it was not feasible to conduct a systemic nationwide sampling procedure during this period, the researchers opted to use an online survey. Malaysian Citizens 18 years old and who are currently staying in Malaysia during MCO 2.0 are eligible to participate in the survey. A few techniques are used to reach as many respondents as possible all over Malaysia within a month. Three main platforms were used in disseminating this survey by using social media which are WhatsApp, Facebook and Telegram. WhatsApp message with the standardised general description about the survey was provided before the link was given in both English and Malay language versions of the questionnaire. A total data of 419 respondents have been collected.

### **Study instrument**

The survey instrument was adapted from a study on knowledge, attitudes and practices towards COVID-19 in Malaysia [7]. The questionnaire consisted of four main themes: 1) Demographics which study respondents' socio-demographic information, including gender, race, age, marital status, education, occupation, place of current residence and regional; 2) Knowledge about COVID-19; 3) Attitudes towards COVID-19; 4) Practices relevant to COVID-19. The questionnaire was given in the English and Malays languages versions.

To measure knowledge about COVID-19, 11 items were adapted from the previous research [7]. These items include the participant knowledge about clini-

cal presentations (items 2-5), transmission routes (items 6-9), the incubation period (item 10) and mortality rate (item 11). "Yes" or "No" response options were given to the participants to these items. 1 point was assigned as a correct response to items while 0 point was assigned as an incorrect response. The range from 0-11 is the maximum total score, with a higher score (9-12) indicating good knowledge, a score of 5-8 indicating moderate knowledge and a score of 1-4 indicating poor knowledge.

To measure attitudes towards COVID-19, study participants were assessed whether they agree (yes) or disagree (no) this MCO affected their tradition, psychology, studies and occupation. Also, to evaluate their opinions regarding the conspiracy of COVID-19. The range from 0-10 is the maximum total score, with a higher score (7-10) indicating good attitude, a score of 4-6 indicating moderate attitude and a score of 1-3 indicating poor attitude. Meanwhile, to measure practices, the study participants were asked whether they wore a face mask outside, practised proper hand hygiene and social distancing at public places. The range from 0-10 is the maximum total score, with a higher score (7-10) indicating good practice, a score of 4-6 indicating moderate practice and a score of 1-3 indicating poor practice.

### Statistical analysis

The data was analyzed using Statistical Package for the Social Science (SPSS) software version 26.

Frequencies and percentages were determined using descriptive analysis. The reliability of the variables was tested by using the Cronbach alpha coefficient to determine the internal consistency of Knowledge, Attitude and Practice. The results showed that Cronbach alpha for knowledge (11 items) was 0.340, attitude (10 items) was 0.413 and practices (9 items) was 0.469. Independent T-test and One-way analysis of variance (ANOVA) followed by post-hoc Tukey test were used to determine the significant level of means (dependent variables) for demographics. Chi-square was used to determine the correlation between independent and dependent variables. *P* value that is less than 0.05 will be considered significant.

## RESULTS

### Sociodemographic characteristics of participants

This study involved 419 numbers of participants. The majority of the study participants 240 (57.3%) were females and 395 (94.3%) were Malays. Most of the participants were aged between 18 and 29 years old with 40.6% (170), 241 (57.5%) were married, 198 (47.3%) possessed Bachelor's degree, 208 (49.6%) were employed, 290 (69.2%) resided in urban areas and 134 (32.1%) came from Southern Malaysia. Other demographics are enumerated in Table 1.

Table 1: Demographic characteristics of participants (N=419).

Characteristics		Number	Percentage (%)
Gender	Male	179	42.7
	Female	240	57.3
Race	Malays	395	94.3
	Chinese	10	2.4
	Indian	9	2.1
	Others	5	1.2
Age	18-29	170	40.6
	30-39	49	11.7
	40-49	89	21.2
	50-59	90	21.5
	>60	21	5.0
Marital status	Married	241	57.5
	Single	169	40.3
	Others	9	2.1
Education	SPM	59	14.1
	Pre-University and its equivalent	87	20.8
	Bachelor's degree	198	47.3
	Master's degree	42	10.0
	PhD	13	3.1
	Others*	20	4.8
Occupation	Employed	208	49.6
	Unemployed	32	7.6
	Student	132	31.5
	Retired	47	11.2
Place of current residence	Urban	290	69.2
	Rural	129	30.8
Regional	Central	62	14.8
	Northern	124	29.6
	Southern	134	32.0
	Eastern	93	22.0
	Sabah/Sarawak	6	1.4

\*"Others" includes educations such as Diploma.

\*\*"Others" includes marital status such as widow and widower.

### Assessment of knowledge

A total of eleven questions were used to measure knowledge of the COVID-19 virus. The average knowledge score for participants was 9.296 (SD = 1.148, range 0–11). The overall correct answer rate of the knowledge questionnaire was 84.5% (9.296/11\*100) while the range of correct answer rates for all participants were between 1.7% to 100%. About 50.8% of participants were able to obtain scores above 9, representing an acceptable level of knowledge on COVID-19 (Table 2).

Most participants knew that there is currently no effective cure for COVID-19, but early, symptomatic and supportive treatment could help most patients recover from the infection and the mortality rate of COVID-19 patients in the elderly is higher than adults and children 408 (97.4%). Only 325 (77.6%) of participants answered correctly when asked unlike the common cold, stuffy nose, runny nose, and sneezing were less common in a person infected with the COVID-19 virus and just 280 (66.8%) answered correctly when asked eating or touching wild animals would result in the infection by the COVID-19 virus.

Differences in knowledge scores among different demographic characteristics were assessed using t-tests and ANOVA. The results showed that knowledge scores were significantly different across races. Higher knowledge scores were obtained among Malay participants 395 (94.3%) as shown in Table 3.

Association of knowledge category among different demographic characteristics were assessed using

Chi-square test. The results showed that knowledge category was significantly associated across races and regions. 311 (78.7 %) of Malay participants have better knowledge as compared to other races. Additionally, study participants who are living in the eastern region of Malaysia 81 (871.1%) have good knowledge than those who are living in other regions of Malaysia.

### Assessment of attitudes

Participants were asked ten questions in the assessment of attitudes towards COVID-19. Some positive attitudes were observed, for example, the majority of respondents 381 (90.9%) stated that MCO 2.0 was needed to prevent the transmission of COVID-19. 361 (88.1%) were afraid and had a feeling of restlessness when going out during COVID-19 pandemic, and 360 (85.9%) agreed to implement Enhanced Movement Control Order (EMCO) if their residents are infected by COVID-19. Additionally, almost all respondents 403 (96.2%) reported that the COVID-19 pandemic had caused events (e.g. feast, birthday party) to not be held even though it is Malaysian's tradition. The distribution of responses from participants for each attitude question is presented in Table 4.

The results showed that attitudes scores were significantly different across races, ages, marital status, occupation and regional. Higher attitudes scores were obtained among 395 (93.5%) Malays, 170 (37.5%) people aged 18-29, 241 (60.3%) married, 198 (47.8%) bachelor's degree, 208 (50.5%) employed and 134 (30.8%) participants who resides in southern region of Malaysia (Table 5).

Table 2: Participant knowledge of COVID-19 (N=419)

Knowledge questions	Frequency	
	YES	NO
COVID-19 originated from Wuhan, China.	<b>404</b> <b>(96.4%)</b>	15 (3.6%)
The main clinical symptoms of COVID-19 are fever, fatigue, dry cough and body aches.	<b>389</b> <b>(95.0%)</b>	21 (5.0%)
Unlike the common cold, stuffy nose, runny nose, and sneezing are less common in person infected with the COVID-19 virus.	<b>325</b> <b>(77.6%)</b>	94 (22.4%)
There currently is no effective cure for COVID-19, but early, symptomatic and supportive treatment can help most patients recover from infection.	<b>408</b> <b>(97.4%)</b>	11 (2.6%)
Not all person with COVID-19 will develop to severe cases. Only those who are elderly and have chronic illnesses are more likely to be severe cases.	<b>377</b> <b>(90.0%)</b>	42 (10.0%)
Eating or touching wild animals would result in the infection by the COVID-19 virus.	139 (33.2%)	<b>280</b> <b>(66.8%)</b>
Persons with COVID-19 cannot infect the virus to others if they do not have a fever.	43 (10.3%)	<b>376</b> <b>(89.7%)</b>
The COVID-19 virus spreads via respiratory droplets of infected individuals.	<b>379</b> <b>(90.5%)</b>	40 (9.5%)
The COVID-19 virus is airborne.	<b>280</b> <b>(66.8%)</b>	139 (33.2%)
Incubation period of COVID-19 is 14 days.	<b>401</b> <b>(95.7%)</b>	18 (4.3%)
Mortality rate of COVID-19 patients in elderly is higher than adults and children.	<b>408</b> <b>(97.4%)</b>	11 (2.6%)

Correct answers are indicated in bold.

Table 3: Demographic of participants, knowledge score and knowledge category.

Demographic		No. of participants	Knowledge score (Mean $\pm$ SD)	Knowledge category (% within group)			p-value
				Poor	Moderate	High	
Gender	Male	179 (42.7%)	9.302 $\pm$ 1.271	0 (0%)	42 (23.5%)	137 (76.5%)	p>0.05
	Female	240 (57.3%)	9.292 $\pm$ 1.050	0 (0%)	53 (22.1%)	187 (77.9%)	
Race	Malay	395 (94.3%)	9.337 $\pm$ 1.131*	0 (0%)	84 (21.3%)	311 (78.7%)	p<0.05
	Chinese	10 (2.4%)	8.000 $\pm$ 1.333*	0 (0%)	7 (70%)	3 (30%)	
	Indian	9 (2.1%)	9.111 $\pm$ 1.654	0 (0%)	2 (22.2%)	7 (77.7%)	
	Others	5 (1.2%)	9.000 $\pm$ 1.000	0 (0%)	2 (40%)	3 (60%)	
Age	18-29	170 (40.6%)	9.188 $\pm$ 1.240	0 (0%)	45 (26.5%)	125 (73.5%)	p>0.05
	30-39	49 (11.7%)	9.350 $\pm$ 1.182	0 (0%)	9 (18.4%)	40 (81.6%)	
	40-49	89 (21.2%)	9.348 $\pm$ 1.046	0 (0%)	19 (21.3%)	70 (78.7%)	
	50-59	90 (21.5%)	9.422 $\pm$ 1.060	0 (0%)	19 (21.1%)	71 (78.9%)	
	Above 60	21 (5%)	9.286 $\pm$ 1.102	0 (0%)	3 (14.3%)	18 (85.7%)	
Marital status	Married	241 (57.5%)	9.378 $\pm$ 1.104	0 (0%)	50 (20.7%)	191 (79.3%)	p>0.05
	Unmarried	169 (40.3%)	9.207 $\pm$ 1.200	0 (0%)	42 (24.9%)	127 (75.1%)	
	Others	9 (2.1%)	8.778 $\pm$ 1.202	0 (0%)	3 (33.3%)	6 (66.7%)	
Education	SPM	59 (14.1%)	9.424 $\pm$ 1.004	0 (0%)	12 (20.3%)	47 (79.7%)	p>0.05
	Pre-University and its equivalent	88 (21%)	9.455 $\pm$ 1.203	0 (0%)	20 (22.7%)	68 (77.3%)	
	Bachelor's Degree	198 (47.3%)	9.202 $\pm$ 1.162	0 (0%)	47 (23.7%)	151 (76.3%)	
	Master	42 (10%)	9.262 $\pm$ 1.231	0 (0%)	11 (26.2%)	31 (73.8%)	
	Others	32 (7.6%)	9.250 $\pm$ 1.047	0 (0%)	5 (15.6%)	27 (84.4%)	
Occupation	Employed	288 (49.6%)	9.341 $\pm$ 1.083	0 (0%)	42 (20.2%)	166 (79.8%)	p>0.05
	Unemployed	32 (7.6%)	9.500 $\pm$ 1.164	0 (0%)	6 (18.8%)	26 (81.3%)	
	Student	132 (31.5%)	9.152 $\pm$ 1.251	0 (0%)	38 (28.8%)	94 (71.2%)	
	Retired	47 (11.2%)	9.362 $\pm$ 1.111	0 (0%)	9 (19.1%)	38 (80.9%)	
Residence	Urban	290 (69.2%)	9.286 $\pm$ 1.133	0 (0%)	69 (23.8%)	221 (76.2%)	p>0.05
	Rural	129 (30.8%)	9.318 $\pm$ 1.186	0 (0%)	26 (20.2%)	103 (79.8%)	
Regional	Central	62 (14.8%)	9.081 $\pm$ 1.135	0 (0%)	17 (27.4%)	45 (72.6%)	p>0.05
	Northern	124 (29.6%)	9.307 $\pm$ 1.156	0 (0%)	29 (23.4%)	95 (76.6%)	
	Southern	134 (32%)	9.261 $\pm$ 1.117	0 (0%)	32 (25.4%)	100 (74.6%)	
	Eastern	93 (22.2%)	9.505 $\pm$ 0.983	0 (0%)	12 (12.9%)	81 (87.1%)	
	Sabah & Sarawak	6 (1.4%)	8.833 $\pm$ 1.148	0 (0%)	3 (50%)	3 (50%)	

\*\*Others" includes educations such as Diploma.

\*\*Others" includes marital status such as widow and widower.

Table 4: Frequency of response for attitude questions of participants in Malaysia.

Attitude questions	Frequency	
	Yes	No
In your opinion, is MCO 2.0 needed to prevent the transmission of COVID-19?	<b>381 (90.1%)</b>	38 (9.1%)
In your opinion, if your residential are infected by Covid-19, is Enhanced Movement Control Order (EMCO) needed?	<b>360 (85.9%)</b>	59 (14.1%)
In your opinion, does COVID-19 pandemic caused students need not to go to school/universities?	<b>328 (78.3%)</b>	91 (12.3%)
In your opinion, does COVID-19 pandemic caused places of worship to be closed?	<b>188 (44.9%)</b>	231 (55.1%)
In your opinion, does COVID-19 pandemic caused events (e.g. feast, birthday party) to not be held even though it is Malaysia's traditions?	<b>403 (96.2%)</b>	16 (3.8%)
In your opinion, does COVID-19 pandemic cause you restlessness and fright when going out?	<b>369 (88.1%)</b>	50 (11.9%)
In your opinion, does COVID-19 pandemic cause difficulties for you to maintain your job?	<b>297 (70.9%)</b>	122 (29.1%)
In your opinion, is the COVID-19 virus an agenda from an organization?	153 (36.5%)	<b>266 (63.5%)</b>
In your opinion, does MCO 2.0 cause a person to commit suicide?	181 (43.2%)	<b>238 (56.8%)</b>
In your opinion, does pandemic Covid-19 caused difficulties for students in online learning?	345 (82.3%)	<b>74 (17.7%)</b>

Correct answers are indicated in bold

The results found a significant association of attitude across age, marital status and occupation. 14 (66.7%) people aged more than 60 years old have better attitudes than other age groups. 'Others' marital status people also showed better attitudes rather than married and single people. Furthermore, 21 (44.7%) retired people showed better attitudes as compared to occupation status.

### Assessment of practices

From an online survey, 9 questions were developed to evaluate Malaysian practice toward COVID-19. This includes prevention efforts, responsibility, cleanliness, and a healthy lifestyle. The majority of the respondents 415 (99%) are very responsible for wearing masks when going out. Most of them 405 (96.7%) do wash or sanitize their hands before and after going somewhere else. For the third question, 397 (94.7%) of participants noted that they try to avoid crowded places like banks, mosques, and night markets. When the respondents were asked whether they encourage their family or friends to follow the current SOP, the majority of the 408 (98.6%) did say yes. Moreover, 403 (96.2%) of the respondents try to avoid confined spaces like surau, ATM, lift and lecture hall.

Furthermore, 408 (97.4%) of respondents practice social distancing in daily life. In good times, 394 (94%) of them try to avoid close conversations with other people as they do not want to get easily infected. Last but not least, when the participants were asked whether they usually go to crowded or confined places, most of them 389 (92.8%), would not go as they are aware that poorly ventilated places have a high risk of infection (Table 6).

The results showed that attitudes scores were significantly different in gender, education, occupation and regional. Higher practice scores were obtained among 240 (58.1%), 198 (47.8%)

Bachelor's degree, 208 (49.2%) employed and 134 (31.1%) participants who reside in southern regions of Malaysia (Table 7).

The results showed a significant association of practices across gender, education and regional. 187 (77.9%) females have good practices towards COVID-19 as compared to males. 'Others' education background participants 27 (84.4%) showed good practices than people with SPM, pre-university, Bachelor's degree, Master's degree and PhD. Furthermore, good practices are also shown by participants who are living in the eastern region of Malaysia 81 (87.7%) than participants from the other regions of Malaysia.

### DISCUSSIONS

The large number of Malaysians with high scores in knowledge indicated that information on COVID-19 was successfully delivered to the public despite them being in rural areas. Public television, newspapers, the official portal of the Ministry of Health (MOH) and Telegram official account of MOH are the media sources on COVID-19 information. Mobile vans which helped to spread information on COVID-19 was one of the effective initiatives to increase awareness among the public especially in the rural areas, where internet access is limited [11]. This was done by the Department of Information Malaysia with the collaboration of MOH. On the other hand, social networks always become a threat to Malaysians because of their misinformation which may explain why there were numbers of Malaysians with moderate knowledge [12].

The study reported that there was a significant association between races (Malay and Chinese)

Table 5: Demographic of participants, attitude score and attitude category.

Demographic		No. of participants	Attitude score (Mean ± SD)	Attitude category			p-value
				Poor	Moderate	High	
Gender	Male	179 (42.7%)	5.749±1.568	11 (6.1%)	114 (63.7%)	54 (30.2%)	p>0.05
	Female	240 (57.3%)	5.754±1.461	17 (7.1%)	148 (61.9%)	74 (31.0%)	
Race	Malay	395 (94.3%)	5.704±1.508	28 (7.1%)	251 (63.7%)	115 (29.2%)	p>0.05
	Chinese	10 (2.7%)	6.600±0.966	0 (0.0%)	5 (50.0%)	5 (50.0%)	
	Indian	9 (2.1%)	6.333±1.225	0 (0.0%)	4 (44.4%)	5 (55.6%)	
	Others	5 (1.4%)	6.800±1.924	0 (0.0%)	2 (40%)	3 (60%)	
Age	18-29	170 (37.5%)	5.312±1.460*	18 (10.6%)	117 (68.8%)	35 (20.6%)	p<0.05
	30-39	49 (12.0%)	5.878±1.495	30 (61.2%)	9 (18.4%)	15 (30.6%)	
	40-49	89 (21.2%)	5.742±1.483*	4 (4.5%)	56 (63.6%)	28 (31.8%)	
	50-59	90 (23.5%)	6.289±1.256*	2 (2.2%)	52 (57.8%)	36 (40.0%)	
	Above 60	21 (5.9%)	5.752±1.506*	0 (0.0%)	7 (33.3%)	14 (66.7%)	
Marital status	Married	241 (60.3%)	6.029±1.470*	10 (4.2%)	140 (58.3%)	90 (37.5%)	p<0.05
	Unmarried	169 (37.3%)	5.314±1.452*	18 (10.7%)	117 (69.2%)	34 (20.1%)	
	Others	9 (2.4%)	6.556±1.509	0 (0.0%)	5 (55.6%)	4 (44.4%)	
Education	SPM	59 (13.9%)	5.695±1.545	2 (3.4%)	40 (69.0%)	16 (27.6%)	p>0.05
	Pre-University and its equivalent	87 (19.6%)	5.425±1.522	11 (12.6%)	55 (63.2%)	21 (24.1%)	
	Bachelor's Degree	198 (47.8%)	5.813±1.378	11 (5.6%)	124 (62.6%)	63 (31.8%)	
	Master	42 (10.8%)	6.191±1.596	2 (4.8%)	25 (59.5%)	15 (35.7%)	
	Phd	13 (3.2%)	5.923±1.656	0 (0.0%)	8 (61.5%)	5 (38.5%)	
	Others	20 (4.7%)	5.700±2.055	2 (10.0%)	10 (50.0%)	8 (40.0%)	
Occupation	Employed	208 (49.6%)	5.851±1.472	12 (5.8%)	128 (61.5%)	68 (32.7%)	p<0.05
	Unemployed	32 (7.5%)	5.656±1.825	3 (9.7%)	17 (19.4%)	11 (35.5%)	
	Student	132 (29.5%)	5.379±1.417	13 (9.8%)	91 (68.9%)	28 (21.2%)	
	Retired	47 (12.5%)	6.426±1.410	0 (0.0%)	26 (55.3%)	21 (44.7%)	
Residence	Urban	290 (69.2%)	5.779±1.490	21 (7.2%)	178 (61.4%)	91 (31.4%)	p>0.05
	Rural	128 (30.8%)	5.752±1.545	7 (5.5%)	84 (65.6%)	37 (28.9%)	
Regional	Central	62 (14.8%)	6.097±1.457	3 (4.8%)	35 (56.5%)	24 (38.7%)	p>0.05
	Northern	124 (29.6%)	5.613±1.601	13 (10.5%)	75 (60.5%)	36 (38.7%)	
	Southern	133 (32%)	5.545±1.530	10 (7.5%)	89 (66.9%)	34 (25.6%)	
	Eastern	93 (22.2%)	5.979±1.277	2 (2.2%)	59 (63.4%)	32 (34.4%)	
	Sabah & Sarawak	6 (1.4%)	6.167±2.041	0 (0.0%)	4 (66.7%)	2 (33.3%)	

\*\*Others" includes education such as Diploma.

\*\*Others" includes marital status such as widow and widower.



Table 6: Frequency of response for practice questions of study participants in Malaysia.

Question	Frequency	
	Yes	No
Do you wear mask when go out?	<b>415 (99.0%)</b>	4 (1.0%)
Do you wash or sanitize hands before and after going somewhere else?	<b>405 (96.7%)</b>	14 (3.3%)
Do you try to avoid crowded places? eg: bank, mosque, and night market?	<b>397 (94.7%)</b>	22 (5.3%)
Do you encourage your family/friend to follow the current SOP?	<b>413 (98.6%)</b>	6 (1.4%)
Do you try to avoid confine spaces? (e.g Surau, ATM, lift, lecture hall)	<b>403 (96.2%)</b>	16 (3.8%)
Do you practice social distancing in daily life?	<b>408 (97.4%)</b>	11 (2.6%)
Are you willing to pay the compound for not complying the SOP?	<b>103 (24.6%)</b>	316 (75.4%)
Do you try to avoid close conversation with other people?	<b>394 (94%)</b>	25 (6%)
Do you usually go to crowded/confined place?	30 (7.2%)	<b>389 (92.8%)</b>

Correct answers are indicated in bold.

and knowledge. The finding was unexpected as there was no study done yet regarding races and knowledge on COVID-19 in Malaysia. This was primarily due to the language barrier of Chinese who could not understand Bahasa Malaysia or even English [13]. This has become a problem since most of the source information is delivered in Bahasa Malaysia and English. However, there was still news and information provided in Mandarin such as TV2 news on television, Mandarin newspaper and Mandarin option in the official portal of MOH.

There was no significant association between attitude and gender. This finding showed the contradictory result from the study in America by Sarria-Guzmán et al. (2021) where females have more good attitudes due to women having good knowledge [14]. While in Malaysia, the results from this study showed that the percentage of every gender against attitude has not fluctuated differently between both genders. This study indicated that the same level of attitudes among races in Malaysia is not significant between race and attitude. Thus, this result showed that attitude did not depend on race.

The age group was significantly associated with attitude. This study showed that a group of people older than 60 has a higher good attitude compared to the moderate attitude and has a good attitude rather than a poor and moderate attitude. The findings in this study contradicted the study conducted by Haque et al. (2021), but showed an attitude significantly associated with the age group where people who aged more than 30 years old in Bangladesh have a good attitude beginning in the third decade of their age in the population. There is a significant association between marital status and attitude based on this study, the result showed that other marital statuses have a higher good attitude compared to married and single people. This result is the same as the previous study conducted by [15] where the result also showed that marital status is significantly associated with attitude.

Based on a study in America, where women with higher education levels resulted in a good attitude, which means it is different from Malaysia where most Malaysian citizens mostly have a moderate attitude in any different level of education. This result indicated that occupation was associated with attitude, where retired people have more good attitudes than employed, unemployed and students in Malaysia because retired people mostly were 60 years old, and above which are associated with age groups that also result in good attitudes. Most other countries in the world, like America, where women with rewarded employment and higher education levels resulted in good attitudes [14].

In this study, there was no significant association between places of current residence because the result between rural and urban is quite the same where the most people in these two residences indicates moderate attitude. These findings concluded that this study differed from the study by Zhong B. L et al. (2020) in which current residence and attitude are significantly associated [15]. A study from Azlan et al. (2020) in Malaysia during Movement Restricted Order (MCO) 2020 indicated that regional has significantly associated with attitude [7], while this study in 2021 during MCO 2.0 indicated that regional has no association with attitude ( $p > 0.05$ ).

Regardless of whether a small sample size provided a good research output [16] it was predicted that the sample size in this study was considered large enough and has its significant influence [17]. Regarding the studies on Indonesia's KAP level, most of their students had acted negatively during the pandemic situation [18]. Meanwhile, based on this study showed that most of the Malaysians carried out the practice towards COVID-19 very well. It is proved that 98.8% of the participants are classified as good practice because they would score more than 5 marks in the online survey.

Table 7: Demographic of study participants, practice score and practice category.

Demographic		No. of participants	Practice score (Mean $\pm$ SD)	Practice category			p-value
				Poor	Moderate	High	
Gender	Male	179 (42.7%)	7.782 $\pm$ 1.013*	0 (0.0%)	42 (23.5%)	137 (76.5%)	p<0.05
	Female	240 (57.3%)	8.058 $\pm$ 0.735*	0 (0.0%)	53 (22.1%)	187 (77.9%)	
Race	Malay	395 (94.3%)	7.924 $\pm$ 1.013	0 (0.0%)	84 (21.3%)	311 (78.7%)	p>0.05
	Chinese	10 (2.4%)	8.500 $\pm$ 0.707	0 (0.0%)	7 (70%)	3 (30%)	
	Indian	9 (2.1%)	8.111 $\pm$ 0.601	0 (0.0%)	2 (22.2%)	7 (77.7%)	
	Others	5 (1.2%)	7.800 $\pm$ 0.447	0 (0.0%)	2 (40%)	3 (60%)	
Age	18-29	170 (40.6%)	7.977 $\pm$ 0.973	0 (0.0%)	45 (26.5%)	125 (73.5%)	p>0.05
	30-39	49 (11.7%)	7.918 $\pm$ 0.786	0 (0.0%)	9 (18.4%)	40 (81.6%)	
	40-49	89 (21.2%)	7.820 $\pm$ 0.972	0 (0.0%)	19 (21.3%)	70 (78.7%)	
	50-59	90 (21.5%)	8.022 $\pm$ 0.636	0 (0.0%)	19 (21.1%)	71 (78.9%)	
	Above 60	21 (5%)	7.857 $\pm$ 0.655	0 (0.0%)	3 (14.3%)	18 (85.7%)	
Marital status	Married	241 (57.5%)	7.888 $\pm$ 0.806	0 (0.0%)	50 (20.7%)	191 (79.3%)	p>0.05
	Unmarried	169 (40.3%)	7.988 $\pm$ 0.970	0 (0.0%)	42 (24.9%)	127 (75.1%)	
	Others	9 (2.1%)	8.444 $\pm$ 0.527	0 (0.0%)	3 (33.3%)	6 (66.7%)	
Education	SPM	59 (14.1%)	7.593 $\pm$ 1.275*	0 (0.0%)	12 (20.3%)	47 (79.7%)	p<0.05
	Pre-University and its equivalent	88 (21%)	8.011 $\pm$ 0.856*	0 (0.0%)	20 (22.7%)	68 (77.3%)	
	Bachelor's Degree	198 (47.3%)	8.025 $\pm$ 0.664*	0 (0.0%)	47 (23.7%)	151 (76.3)	
	Master	42 (10%)	8.048 $\pm$ 0.539	0 (0.0%)	11 (26.2%)	31 (73.8%)	
	Others	32 (7.6%)	8.000 $\pm$ 0.918	0 (0.0%)	5 (15.6%)	27 (84.4%)	
Occupation	Employed	288 (49.6%)	7.865 $\pm$ 0.938	0 (0.0%)	42 (20.2%)	166 (79.8%)	p>0.05
	Unemployed	32 (7.6%)	7.781 $\pm$ 1.157	0 (0.0%)	6 (18.8%)	26 (81.3%)	
	Student	132 (31.5%)	8.106 $\pm$ 0.754	0 (0.0%)	38 (28.8%)	94 (71.2%)	
	Retired	47 (11.2%)	7.914 $\pm$ 0.583	0 (0.0%)	9 (19.1%)	38 (80.9%)	
Residence	Urban	290 (69.2%)	7.900 $\pm$ 0.877	0 (0.0%)	691 (23.8%)	221 (76.2%)	p>0.05
	Rural	129 (30.8%)	8.031 $\pm$ 0.865	0 (0.0%)	26 (20.2%)	103 (79.8%)	
Regional	Central	62 (14.8%)	8.016 $\pm$ 0.665	0 (0.0%)	17 (27.4%)	45 (72.6%)	p<0.05
	Northern	124 (29.6%)	7.984 $\pm$ 0.826	0 (0.0%)	29 (23.4%)	95 (76.6%)	
	Southern	134 (32%)	7.731 $\pm$ 1.125*	0 (0.0%)	32 (25.4%)	100 (74.6%)	
	Eastern	93 (22.2%)	8.140 $\pm$ 0.563*	0 (0.0%)	12 (12.9%)	81 (87.1%)	
	Sabah & Sarawak	6 (1.4%)	7.833 $\pm$ 0.408	0 (0.0%)	3 (50%)	3 (50%)	

\*\*Others" includes educations such as Diploma.

\*\*Others" includes marital status such as widow and widower.

The increasing level of good practice among the Malaysians was due to the government having done a very good job in handling the crisis of COVID-19 by spreading awareness through all possible platforms [7]. Thus, Malaysian citizens had no excuse for not carrying the responsibility. Moreover, based on a previous study in Bangladesh, a developing country with ~163 million population (2019), indicated that most of the population there are not well aware of COVID-19 crisis, so they are still some of them were not practising well to avoid the upcoming hazardous situation [19]. Contrary to Malaysia, which is a developed country with ~32.73 million population (2021), Malaysians are well prepared with the knowledge, so they are aware of how to do the practice.

There was a significant association between practices and gender. Female 97.9% good at practice compared to the male which is 93.9%. Our findings were similar to a study conducted in China by Xue, B., & McMunn, A. (2021) showed females have better practices compared to males [20]. This happens because females have more awareness toward COVID-19 compared to the male who did not apply good practice through the pandemic. For the male, three have poor practices, eight have moderate and 168 have good practices meanwhile in females, none has poor practices, five have moderate and 235 females have good practices.

The finding in this study was almost similar to the research conducted by Azlan et al. (2020) that showed people age 50 and above have best practices compared to lower ages [7]. This happened because older people may feel afraid of deadly Coronavirus compared to younger people. To be specific, 21 people aged 60 and above have good practices. For 50 -59, two people are moderate and 88 have good practices. For 40-49, one person has poor practice, four have moderate and 84 have good practice. For 30 – 39, two people have moderate practice and 47 people have good practices. For (18-29), two have poor, five have moderate and 163 have a good practice.

Our findings contradicted the study in China that was conducted by Zhong, B. L. (2020) [15]. Of 241 married people, one has poor practice, eight have moderate and 232 have a good practice. Meanwhile, two single people have poor practices, five moderate and 162 have good practices. For the other nine people, they all have good practices.

Our finding was similar to research conducted by Azlan et al. (2020) [7]. This happens because retired people were the smart people before they retired, so they must be the type of people who followed SOP. For the employed people, three have poor practices, seven have moderate and 198 have good practices. For the unemployed, three people have moderate practices and 29 people have good practices. For students, three people have moderate practices and 129 have good practices and 47 people who are retired are having good practices.

The finding of this study was similar to the one that

was conducted in China by Xue, B., & McMunn, A. (2021) [20]. Their study showed that the higher level education, the better the practices. This happened because they might have a good understanding of COVID-19 virus. For SPM level, two people have poor practices, four moderate and 53 good. Meanwhile, pre-university and equivalent, three moderate and 84 good. For Bachelor's degree, four moderate and 194 have good practice. For a Master's degree, all 42 people have good practices. For PhD, one have poor practices and 12 have good practices.

Our findings are correlated with the study conducted by Azlan et al. (2020) [7]. In a similar study that showed Sabah/Sarawak has good practices 75% compared to Southern 73.3%. This happened because the people in Sabah & Sarawak have faced the highest cases before, so they have more awareness. For the central, one person has moderate practices and 61 good practices. For Northern, six people have moderate practices and 118 people have good practices. For Southern, three people have poor practices, six people moderate and 125 people have good practices. In the Eastern, all 93 people have good knowledge. For Sabah/Sarawak, all six people have good knowledge.

Our findings were similar to research conducted by Xue, B., & McMunn, A. (2021) [20]. People who lived in rural areas had good practices because they were not busy like the people who lived in urban areas that broke many SOP to achieve their goals. In this research, three people from urban areas have poor practice, nine moderate and 278 people have a good practice. Meanwhile, in rural areas, four people have moderate practices and 125 people have good practices.

## CONCLUSION

In conclusion, most Malaysians have a good knowledge and moderate attitudes with good practice in reacting to COVID-19 outbreak. Good knowledge of Malaysian citizens has contributed to the success of delivering information on COVID-19. This study also showed a significant association between age groups with attitude and practice. Good attitude was also demonstrated by retired people compared to employed, unemployed and students. Furthermore, about 98.8% of the participants from this study have good practice towards COVID-19. It is due to excellent management from the government in handling the crisis of COVID-19 by spreading awareness through all possible platforms. The higher of knowledge is the better practices among Malaysian towards COVID-19.

## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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Original Article

KNOWLEDGE, ATTITUDE AND PRACTICE OF SCREEN TIME AMONG UNDERGRADUATE UNIVERSITY STUDENTS IN MALAYSIA DURING PANDEMIC

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ABSTRACT

The usage of electronic devices is on the rise during the COVID-19 pandemic. This is very relevant especially to university students where e-learning has been introduced to substitute face-to-face learning. This study evaluated the knowledge, attitude and practice of screen time among undergraduate university students in Malaysia. A cross-sectional study was conducted. Undergraduate university students aged 18 or more were interviewed using a structured questionnaire regarding the socio-demographic information, knowledge, attitude and practice of screen time during the pandemic. A total of 388 participants were recruited from March to July 2021. More than 95% of participants had adequate knowledge and around 51% had a favourable attitude towards screen time. Despite high percentages of knowledge and attitude, only about 10% of the participants had good practice of screen time during this pandemic. There was a significant portion of female students who had better knowledge and attitude of screen time compared to male students ( $p < 0.05$ ). In conclusion, the knowledge and attitude of screen time were adequate among the undergraduate university students, but they were not able to put their knowledge into practice possibly due to lifestyle and learning changes that happened during the COVID-19 pandemic. It is crucial to observe their practice after the pandemic ends to investigate the relationship .

INTRODUCTION

Since the first outbreak of the coronavirus disease 2019 (COVID-19) in Wuhan, China, in early December 2019, the disease has rapidly spread across the world. Many sectors have been affected due to this pandemic including educational institutions. Various public health measures have been made to contain the spreading of the virus. Universities and schools were forced to close their campuses during the lockdown period, and affecting more than 1.3 billion learners in 186 countries according to the United Nations Educational, Scientific, and Cultural Organization [1]. As a result, education institutions modified their teaching and learning activities to online platforms to avoid interruptions [2].

Screen time refers to the amount of time someone spends looking at an electronic device with a screen, such as a computer, television, handphone or gaming device [3]. In the United States, children and teenagers spend an average of 7.5 to 9 hours per day engaging in sedentary screen-based activities [4]. This practice has become increasingly relevant during this pandemic where e-learning has been implemented. It is a major concern to everyone since we knew that excessive screen time can affect the developing brain. It has

consequences to the cognitive, motor development, learning, memory, emotional regulation and overall health of a person [5].

It has become inevitable for the community to shut the doors and stay inside during the pandemic. However, it is important for everyone especially children and teenagers to understand the right etiquette while using these screens. Global evidence suggests that increased screen time during the COVID-19 pandemic is associated with various impacts on health outcomes and academic performance of students in general. Multiple pieces of research also have shown adverse physical health especially ophthalmological impacts associated with screen time [6]. In another study, Bahkir FA et. Al (2020), found that the increase in digital screen time during the COVID-19 pandemic lockdown was associated with the slow deterioration of ocular health across all age groups [7]. The development and severity of digital eye strain may also differ among different groups such as in different courses taken by the students [8].

The American Optometric Association recommends the 20-20-20 rule to avoid digital eye strain; take a

break from the screen every 20 minutes and look at something at least 20 metres away for 20 seconds [9]. The objective of this study is to determine the level of knowledge, attitude and practice of screen time among the undergraduate students and later can be useful to improve the situation.

## MATERIALS AND METHODS

### Study design

This is a cross-sectional study involving 388 participants. Informed consent was taken from each participant. Participants were recruited from undergraduate university students from public and private universities in Malaysia. The study was carried out from the end of March 2021 to mid-July 2021.

### Inclusion and exclusion criteria

Undergraduate university students from public and private universities in Malaysia and agreed to participate in the study were included. No exclusion criteria in this study.

### Data collection

The sample size was calculated using the Cochran formula ( $n = Z^2 pq/e^2$ ). The sample of 384 was obtained with 5% of allowable error (e) at 95% of confident interval (CI) or Z in the Cochran formula.

The questionnaire consisted of 4 parts: socio-demographic information, knowledge, attitude and practice (KAP) of screen time. The first part is the socio-demographic questionnaire included 5 questions about socio-demographic characteristics of the participants; age, gender, courses, university and electronic devices that they have. This section provided the baseline data of the participants.

The second part included 7 questions about knowledge on screen time and its effect. The third part was related to attitude toward screen time and the last part was related to the question about screen time practice among the participants.

### Validity and reliability

The questionnaire was delivered in Malay and English language to avoid language barrier. A pilot study was performed involving 30 participants. Any errors have been rectified and later distributed among undergraduate students in Malaysia via social media such as WhatsApp, Facebook and Instagram.

### Statistical analysis

Data analysis was performed using SPSS version 26. The following statistical methods were used in this study; descriptive statistics to describe the socio-demographic of participants and KAP scores, chi-square test to see an association between age, gender and courses with knowledge, attitude and practice of screen time and one-way ANOVA to see the difference of mean between two or more groups.

## RESULTS

A total of 388 participants was recruited for this study. The majority (78.9%) of participants were from the age group of 18-20 years. Male participants were 41.2 % and females were 58.8%. Most of the participants (40.9%) studied medicine and allied health sciences (Table 1). Almost all of the participants own a handphone (98.9%) and a laptop (95.3%).

Table 1: Socio-demographic characteristics of the participants (n =388)

Characteristics	Values (%)
Age	
18-20	306 (78.9)
21-23	63 (16.2)
24-26	8 (2.1)
27-29	5 (1.3)
30 and above	6 (1.5)
Gender	
Male	160 (41.2)
Female	228 (58.8)
Courses	
Medicine & Allied Health Sciences	159 (40.9)
Engineering	38 (9.8)
Economic & Business	35 (9.0)
Education	22 (5.7)
Art & Social Science	25 (6.4)
Science	21 (5.4)
Islamic Studies	10 (2.6)
Others	78 (20.1)
Electronic devices	
Handphone	384 (98.9)
Tablet / Ipad	165 (42.5)
Laptop / Desktop computer	370 (95.3)
Television	187 (48.2)
Game console	32 (8.2)

Table 2 shows the scores of the knowledge, attitude and practice of screen time among the participants. More than 95% of participants had an adequate level of knowledge on screen time but a majority of them had poor practice during the COVID-19 pandemic (89.7%). The participants' attitude scores were ambiguous with approximately 50% participants had favourable attitude while another 50% of them had unfavourable attitude.

Table 3 demonstrates the association between knowledge, attitude and practice with different socio-demographic characteristics of the participants such as age, gender and courses. Age  $\leq 20$  and  $\geq 21$  and courses were not significantly associated with knowledge, attitude and practice. Gender, male vs female participants was significantly associated with knowledge ( $p=0.003$ ) and attitude ( $p=0.000$ ).

## DISCUSSION

This study was conducted within the population of undergraduate students in Malaysia within the age of 18 and above. During the COVID-19 pandemic, specifically during Movement Control Order (MCO), everyone was instructed to stay at home except for emergency purposes that were allowed by the government. This order was one of the mechanisms used to decrease the number of COVID-19 cases by reducing human interactions thus avoiding the spread of the virus from a person to another person. All activities outside of their home were prohibited. The government directed everyone to continue work and study from home except front-liners such as doctors, police and security forces. As a result,

Table 2: Knowledge, attitude and practice score of the participants.

Items	Values (percents)
Knowledge score (n=388)	
Adequate	369 (95.1)
Inadequate	19 (4.9)
Attitude score (n=388)	
Favourable	200 (51.5)
Unfavourable	188 (48.5)
Practice score (n=388)	
Good practice	40 (10.3)
Poor practice	348 (89.7)

Table 3: Association of different variables with knowledge, attitude and practice.

Characteristics	Knowledge		Attitude		Practice	
	Adequate	Inadequate	Favourable	Unfavourable	Good	Poor
Age						
$\leq 20$	291	15 (3.9)	158 (40.7)	148 (38.1)	27 (7.0)	279 (71.9)
$\geq 21$	(75.0)	4 (1.0)	42 (10.8)	40 (10.3)	13 (3.4)	69 (17.8)
p-value	78 (20.1)		0.947		0.063	
	0.993					
Gender						
Male	146	14 (3.6)	58 (14.9)	102 (26.3)	19 (4.9)	141 (36.3)
Female	(37.6)	5 (1.3)	142 (36.6)	86 (22.2)	21 (5.4)	207 (53.4)
p-value	223		0.000		0.396	
	(57.5)					
	0.003					
Courses						
Medicine & Allied Health	151	8 (2.8)	83 (21.4)	76 (19.6)	13 (3.4)	146 (37.6)
Others	(38.9)	11 (2.8)	117 (30.2)	112 (28.9)	27 (7.0)	202 (52.1)
p-value	218		0.830		0.250	
	(56.2)					
	0.918					

this MCO led people to increase their screen time. An example, students had their online classes from morning till evening on weekdays. They have to finish their assignments or projects through online at nights and weekends. At the same time, they also had more time to spend on screen as they played games, scrolled their social media, watched movies and others. All these activities caused an increment in their screen time.

Electronic devices are good and beneficial as they can help us in many ways, however, they can lead to excessive screen time. Thus, screen time needs to be controlled wisely. Therefore, a study was conducted regarding the knowledge, attitude and practices regarding screen time amongst university students in Malaysia during COVID-19 pandemic as this may help them to have good control of screen time daily. From this study, the result found that majority of the participants (95.1%) had adequate knowledge. However, only half of them (51.5%) had a favourable attitude and only a little (10.3%) had a good practice regarding screen time. In contrast to the earlier hypothesis, it was found that different courses had no effects on knowledge, attitude, and practices regarding screen time ( $p>0.05$ ).

On the other hand, there was a difference in the knowledge and attitude between male and female participants, which was statistically significant ( $p<0.05$ ). Female participants had both higher adequate knowledge (60.4%) than male participants (39.6%) and higher favourable attitude (71.0%) than male participants (29.0%). However, there was no significant relationship between gender and practices ( $p>0.05$ ). Both genders had high percentages of poor practices with female students contributed to 53.4% while male students were 36.3%. Knowledge, attitude and practices are not related to each other as there was no significant relationship between them ( $p>0.05$ ).

Ideally, students should not only have a good knowledge and attitude, but it must be reflected in their practices regarding screen time. Each participant should know their limits and realize that poor practices might lead to harm themselves physically and mentally. It is imperative to address the factors, which are playing as obstacles for university students in applying a good practice regarding screen time.

As we know, this COVID-19 pandemic urged everybody to stay at home and reduce movement outside. Therefore, all activities need to be done online, including studying. University students need to spend a lot of time in front of the screen to have the learning sessions, as well as to do their assignments. This cannot be prevented as online learning is the only way to continue studying during the Covid-19 pandemic especially during Movement Control Order (MCO). Moreover, students spent their leisure time playing games, watching movies, interacting with their friends via social media, surfing the internet and many more.

The limitation of this study was there might be some dishonest answers or limitation among the participants as they might refer to any sources when answering the questionnaire specifically regarding the knowledge. Moreover, participants might have different interpretations of the questions since there was no one to explain the questions to ensure each of them had the same understanding. There was no way to know if the participants had understood the questions.

## CONCLUSION

In conclusion, the good practices regarding screen time were meagre among university students during the COVID-19 pandemic, but most of them had adequate knowledge and half had a favourable attitude towards screen time. This study gives an insight into the formulation of strategies to educate students on good practice of screen time, together with the short-term and long-term consequences of screen time. Future research is recommended to investigate changes in students' screen time after the pandemic ends.

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## DECLARATION OF CONFLICT OF INTEREST

The authors report no conflicts of interest.

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Original Article

SCREENING ON THE EFFECT OF POLLUTANTS TO ADULTS LIVING NEAR INDUSTRIAL AREAS IN KEDAH

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ABSTRACT

*This study aims to examine the effect of pollutants on adults living near industrial areas in Kuala Muda district, Kedah. There are a few causes of air pollution mainly being industries, transportation, aerosols, forest fires, and radiation. Above all, main contributors are industries and transportation as chemicals, gasses and toxins are released into the air that we breathe in. This will eventually cause effects to our environment and our health especially in short as well as long term. The general objective of the study is to explore the effect of pollutions from industries in Kuala Muda District. The specific objectives are to determine the symptomatic effect after exposure to pollutants, to identify the type of pollutants and lastly to determine the relationship between distance and source of exposure. The sampling method was random sampling which involved residents of Kuala Muda District with different age groups. The inclusion criteria is respondents from Kuala Muda District, Kedah whereas the exclusion criteria are respondents from different districts and respondents with age below 18 years old.*

INTRODUCTION

Air quality greatly affects our daily lives yet astonishingly little did we know it may affect us in the long run if we are living in this not so clean environment. Factories, big or small do contribute significantly to the air quality that we live in. As air pollution is man-made, no matter how we try to save the earth that we so helplessly depend on, we still contribute some damage to it unknowingly. There are a few causes of air pollution mainly being industries, transportation, aerosols, forest fires, and radiation. Above all, the main contributors are industries and transportation as chemicals, gasses and toxins are released into the air that we breathe in. This will eventually cause effects to our environment and our health especially in the short as well as long term. The government and health authorities are doing the best they can to prevent this, and we shall play our part in saving our planet for the next generation.

Air pollution is one of the pollution that many of us are exposed to on a daily basis. Other types of pollution obviously will affect the population's health too, but air pollution is the type that we face regularly. There are numerous health problems impacted by air pollution such as respiratory and lung problems, difficulty in breathing, coughing, sneezing, headaches, migraines

and fatigue. These symptoms can be irritating but they are the long-term effects that we need to pay extra attention to as we are repeatedly being exposed to them. Furthermore, these can also greatly affect those with compromised immune, young children, the elderly or those with health conditions and thus they need to be worried for.

**Air Quality During Pandemic COVID-19**

Newly emerging virus which was discovered in late 2019 in China has wreaked havoc on the whole world. This coronavirus disease (COVID-19) has continued to spread worldwide and many countries have initiated lockdowns countrywide to prevent further morbidity and mortality associated with COVID-19. Due to the lockdown that has been implemented, there are few positive outcomes that have been noted, especially the air quality nationwide. Studies have been done in several tropical and subtropical countries, and an analysis that includes multiple angles have been performed. This analysis includes air pollution, analysis and evaluation for health effects as well as loss of economy during a lockdown. The countries are India, Brazil, Kenya, Iran, Mexico, Malaysia, Peru, Pakistan, Thailand and also Sri Lanka [3].

Moreover, the Department of Environment Malaysia (Jabatan Alam Sekitar Malaysia) has hourly basis data on the Air Pollution Index or API for before and after during lockdown (movement control order or MCO). This data has shown 68 air quality monitor stations for the fine particulate matter (PM<sub>2.5</sub>). During a lockdown, the concentrations of PM<sub>2.5</sub> showed the highest reduction for up to 58.4%. Multiple areas of the red zone (areas with more than 41 confirmed COVID-19 cases) have reduced the concentration variation up to 28.3% in PM<sub>2.5</sub> [4].

For instance, monthly pattern values have shown that measured air pollutants concentrations for Langkawi, Kedah were elevated in the course of the southwest monsoon especially June to September because of activities of biomass burning. The source of air pollutants in the area was motor vehicles as indicated by NO/NO<sub>2</sub> ratio values which exceeded 2.2 as well as the high values of CO/NO<sub>x</sub> ratio i.e. between 28.3 and 43.6 and SO<sub>2</sub>/NO<sub>x</sub> low ratio values i.e. between 0.04 and 0.12 [1].

The levels of air pollutants in Asian countries, specifically India and China are considerably higher than in developed countries. Major sources of air pollutants are industries, traffics, chemical indoor pollutants, tobacco and also burning of household biomass, leading to an increased burden of pulmonary allergies. A study has highlighted the main constituent for indoor as well as outdoor pollutants and related effects on pulmonary allergic reactions correlated to allergic rhinitis and asthma in the region of Asia-Pacific. There is a pressing need to increase awareness of the public, underlining interventions target, population approval, and action call to policymakers to make changes along with interventions on how to reduce air pollution at levels of community-based [4].

Furthermore, more than 70% of total excretions are caused by vehicle ejections in the metropolitan area during periods of non-haze and they have shown diurnal variations at two peaks of the abovementioned air pollutants with the exception of ozone. The peak at rush hour in the morning is mostly due to vehicle ejections meanwhile the peak at late evening is mostly due to conditions of meteorological, specifically stability of the atmosphere and also the speed of the wind. The major pollutant is a total suspended particulate matter as its concentration at several sites frequently exceeded Guidelines of Recommended Air Quality Malaysia. Overall, the common quality of air in Malaysia has declined since 1970. This has been proved by studies showing that if there is no introduction of successful countermeasures, the ejections of nitrogen oxides, sulphur dioxide, hydrocarbons and carbon monoxide along with particulate matter in 2005 will eventually escalate approximately by 2.12, 1.4, 2.27 and 1.47 times, from the levels in 1992 [2].

## METHODOLOGY

This study had been conducted on adults who were 18 years old and older and had lived near industrial

areas in Kuala Muda District in Kedah, Malaysia. The total populations for Kuala Muda district were 435, 959 as of 2020. Data collection for this study was done using the sampling method i.e. random sampling which involved residents of Kuala Muda District, Kedah with different age groups. Thus, a questionnaire had been sent by Google form using the online platform. The responses that had been recorded were divided into groups and tabulated in Table 1.

Each respondent's status would remain as anonymous as their personal details such as name, identity card number or residential address were not recorded. The information gathered consisted only of their age, gender and living area whether near the Kuala Muda industrial areas or not. The questionnaire used had been developed by professional and medical experts and consisted of several items. These factors were identified through a systematic literature review followed by a pilot study.

The online questionnaire had been created using Google form and the link for the online Google form had been shared to Kuala Muda residents by using social media platforms so that they can have easy access to the questionnaire. The database was used to measure the health effects of air pollutants in residents of Kuala Muda District industrial areas. The respondents needed to answer questions and noted if they experienced any health-related symptoms due to air pollutants.

## RESULTS

Based on the data collected, analyses were performed using IBM SPSS V27. The frequencies of each variable were presented in a table such as socio-demographic characteristics (respondent's gender, race, age group, education level, smoking status, living with smokers). The distributions of health symptoms for people living near the industrial areas were measured using cross-tabulation.

Distance from industrial area versus respiratory symptoms was tested. The distance was distributed into 0 to 10 km, 11 to 20 km and more than 20 km. The respiratory symptoms screened were cough, flu, skin itchiness, eye itchiness and difficulty in breathing. From the findings, the subject living closest to the industrial areas (distance 0 to 10 km) have experienced all the respiratory symptoms as compared to others. Meanwhile, only a few of the subjects living the farthest to the industrial areas experienced some of the symptoms. These findings showed that the subjects closest to the industries are more prone to have respiratory symptoms and health effects in contrast to other subjects.

## CONCLUSION

The study had been carried out with few limitations

Table 1: Sampling

Group	Distribution	Number	Percentage
Gender	Male	63	<p>Legend: Lelaki (Male), Perempuan (Female)</p>
	Female	58	
Race	Malay	106	<p>Legend: Cina, India, Lain-lain, Melayu</p>
	Chinese	10	
	Indian	3	
	Others	2	
Age Group	18 - 25 years old	31	<p>Legend: 18 - 25 tahun, 26 - 33 tahun, 34 - 41 tahun, 42 - 49 tahun, 50 tahun ke atas</p>
	26 - 33 years old	16	
	34 - 41 years old	23	
	42 - 49 years old	20	
	Above 50 years old	31	
Education	Primary School	2	<p>Legend: Diploma, Doktor Falsafah, Sarjana, Sarjana Muda, Sijil, STPM/SPM/PMR, UPSR</p>
	Secondary School	18	
	Higher Education	101	
	* certificate, diploma, bachelor degree, master degree, PhD		
Smoking Status	Yes	17	<p>Legend: Tidak (terus ke Soalan 3), Ya</p>
	No	104	
Living with Smoker	Yes	32	<p>Legend: Tidak, Ya</p>
	No	89	

Table 2: Distance from industrial area vs. respiratory symptoms.

Distance from industrial park	Respiratory Symptoms		
	Cough, Flu & Difficulty Breathing	Skin & Eye Itchiness	All
0 to 10km	69	46	
	71.029	43.971	
	-0.2408	0.3060	115
	0.05798	0.09367	
11 to 20km	7	1	
	4.941	3.059	
	0.9262	-1.1772	8
	0.85784	1.38575	
More than 20km	8	5	
	8.029	4.971	
	-0.0104	0.0132	13
	0.00011	0.00017	
Total	84	52	136
	Chi-Square	DF	
Pearson	2.396	2	
Likelihood Ratio	2.791	2	

as due to pandemic COVID-19 that strike worldwide, Malaysia included, the study was executed by using the online platform i.e. by using Google form. Initially, the sample size calculated for this screening was 384 but due to the changes in the mode of the questionnaire from face to face to the online platform, low sample size was obtained with only 121 respondents. This is because the subjects had very limited access to the internet or the internet connection was not good and they were not familiar with the online system during that time. Hence, there was no sufficient data obtained.

Next, time was also crucial and constraint as with the pandemic outbreak at that time (November 2020), the residents were mostly in lockdown and they were busy with the new task of online learning for kids which they had to assist their kids with online home-schooling, therefore, they did not have time to access the questionnaire as they were exhausted with their new responsibilities at home.

However, we can conclude from the findings that they were some effects on the population and this need to be further confirmed with a better number of respondents and a wider area of concern. Furthermore, in this study, there was a lack of data on air quality for the study area or relevant information regarding the actual emissions from the industries that hinders the full investigation. This had made the

study of the proximity to source method to identify the exposure for residents living in the areas. This proximity method had been widely used as it was quick, easy and inexpensive to assess the health impacts from industries and environmental study.

Nevertheless, the findings were useful for both authorities and populations as a whole for health facts and could help increase better livelihood to overcome this. For good measure, this will also help create health awareness regarding health pollution to the populations so that they can have cleaner and better air to live.

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Original Article

SLEEP DEPRIVATION AMONG MEDICAL STUDENTS IN MALAYSIA

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ABSTRACT

Adequate sleep is crucial to achieve optimal brain's ability to learn and remember. Sleep deprivation adversely affects the brain and cognitive functions and a major source of morbidity. Sleep deprivation is associated with increased risks of hypertension, diabetes, obesity, ischaemic heart disease, stroke, motor vehicle accidents and medical errors. Lack of sleep can be due to lifestyle habits and sleep disorders. This study aimed to investigate the prevalence, related factors and effects of sleep deprivation among medical students in Malaysia. A questionnaire comprising of demographic detail, sleep pattern, sleep behaviour and effects of sleep deprivation was distributed through Google Form. A total of 164 (20.7% male and 79.3% female) medical students age 19 to 26 years old from 13 public and private medical schools in Malaysia answered the questionnaire. All statistical analyses were conducted by using the Statistical Package for Social Science (SPSS) version 24. 65% of respondents perceived they are sleep deprived, 43.9% had insomnia and 34% had parasomnia. The two main factors of sleep deprivation are due to studying or doing homework followed by usage of electronic devices before sleep. Among the sleep deprived medical students there is no relationship between sleep deprivation with gender and the average hours of sleep. Sleep deprivation also results in hindered academic performance. These results strongly support further investigation of the important aspect of medical students' life such as factors that affect the ability to concentrate as well as different aspects in learning and neuropsychology. More parameters can be used including biological markers to analyse the association in order to get precise results.

INTRODUCTION

Sleep deprivation, also known as insufficient sleep or sleeplessness, is the condition of not having enough sleep. It can be either chronic or acute and may vary widely in severity. A chronic sleep-restricted state adversely affects the brain and cognitive function. Sleep deprivation (SD) is a major source of morbidity with widespread health effects including increased risks of hypertension, diabetes, obesity, heart attack, and stroke and many sleep deprivation behaviour that brings together vehicle accidents and medical errors and is therefore an urgent topic of investigation [1].

The clinical study of sleep deprivation is studied based on several tests including performing a face/non-face categorization psychomotor vigilance task (PVT) and electroencephalogram (EEG). Lack of sleep can be due to lifestyle habits and sleep disorders. It is not a secret that a good night's sleep makes people feel better. Sleep gives your body time to rest and recharge, and also be crucial to the brain's ability to learn and remember. During sleep, while the body rests, the brain is busy processing information from the day and forming memories. Hence, if sleep is

deprived, it will disrupt the learning centre and impair the memory process to input new learning skills. Therefore, early diagnosis of sleep disorders is essential to prevent detrimental effects on health.

Specific objectives of this study were to determine the prevalence, factors and effects of sleep deprivation among medical students in Malaysia.

Types of sleep pattern

The nature of sleep difficulty varies greatly between people. Medical students are considered a population that is particularly prone to sleep-related problems. Based on the article by Krystal AD (2005) insomnia is a sleep disorder that regularly affects millions of people worldwide. Someone with insomnia finds it difficult to fall asleep or stay asleep. The Symptoms of insomnia may include difficulty falling asleep, trouble staying asleep, and not feeling restored by sleep [2]. Although it has not been clear that it is possible to identify distinct subtypes of patients by symptom or that distinguishing symptom type affects the course of clinical treatment. This is the classification of insomnia by duration most commonly involves

three categories. The first categories are transient which is no more than a few days. Then, the short-term which up to 3 weeks and the last categories are the long-term which is more than 3 weeks. Insomnia also can be classified into symptom type. There are three symptom categories, first is the difficulty of falling asleep, trouble staying asleep and not feeling restored by sleep [2]. There are several ways that insomnia can be classified that are potentially useful in clinical practice. The main reason for distinguishing insomnia for identifying the associated conditions so that those associated conditions can be treated easily.

Another sleep pattern is parasomnia. Parasomnias are a group of sleep disorders characterized by abnormal, unpleasant motor verbal or behavioural events that occur during sleep or wake to sleep transitions [3]. Parasomnias can occur during non-rapid eye movement (NREM) and rapid eye movement (REM) stages of sleep and are more commonly seen in children than in the adult population. Parasomnias are a group of sleep disorders that are characterized by abnormal, unpleasant motor, verbal or behavioural events that occur during sleep or wake to sleep transitions. Parasomnias can be grouped by the type of behaviours seen or based on the sleep stage from which they occur. The most common non-rapid eye movement parasomnias include somnambulism, confessional arousals, and night terrors. Rapid eye movement parasomnias, particularly rapid eye movement sleep behaviours disorder, have been studied more extensively [4]. Usually, the patient with rapid eye movement behaviours disorder will present with abnormal behaviours during rapid eye movement sleep. In conclusion, it is crucial to understand the characteristics of various parasomnias and their association with medical and sleep-related disorders. Parasomnias are distressful and can disrupt the lifestyle of the patients and others. It is also crucial to reassure the patients and discuss in detail their sleep history and follow the possible diagnostic approach for a complete evaluation.

### **The relationship of learning process and sleep**

Sleep helps learning and memory in two distinct ways. First, a sleep-deprived person cannot focus optimally and therefore cannot learn efficiently. Second, sleep itself has a role in the consolidation of memory, which is essential for learning new information. Although the exact mechanism is not known, learning and memory are often described in terms of three functions. Acquisition refers to the introduction of new information into the brain. Consolidation represents the processes by which a memory becomes stable. Recall refers to the ability to access the information (whether consciously or unconsciously) after it has been stored.

Ellenbogen JM, Payne JD and Stickgold R. (2006) study the role of sleep in learning and memory formation in two ways. The first approach looks at the different stages of sleep (and changes in their duration) in response to learning a variety of new tasks. The second approach examines how sleep

deprivation affects learning. Sleep deprivation can be total (no sleep allowed), partial (either early or late sleep is deprived), or selective (specific stages of sleep are deprived) [5].

The earliest sleep and memory research focused on declarative memory, which is the knowledge of fact-based information, or “what” we know. For example, the capital of France, or what you had for dinner last night. In one research study, individuals engaged in an intensive language course were observed to have an increase in rapid eye movement sleep or REM sleep. This is a stage of sleep in which dreaming occurs most frequently. Scientists hypothesized that REM sleep played an essential role in the acquisition of learned material. Further studies have suggested that REM sleep seems to be involved in declarative memory processes if the information is complex and emotionally charged, but probably not if the information is simple and emotionally neutral.

This study has also focused on sleep and its role in procedural memory which is remembering “how” to do something. For example, riding a bicycle or playing the piano. REM sleep seems to play a critical role in the consolidation of procedural memory. Other aspects of sleep also play a role; motor learning seems to depend on the amount of lighter stages of sleep, while certain types of visual learning seem to depend on the amount and timing of both deep, slow-wave sleep (SWS) and REM sleep.

This study also focuses on the impact that a lack of adequate sleep has on learning and memory. When we are sleep deprived, our focus, attention, and vigilance drift, making it more difficult to receive information. Without adequate sleep and rest, overworked neurons can no longer function to coordinate information properly, and we lose our ability to access previously learned information. Besides, our interpretation of events may be affected. We lose our ability to make sound decisions because we can no longer accurately assess the situation, plan accordingly, and choose the correct behaviour.

## **METHODOLOGY**

### **Study design**

This study is a descriptive and qualitative study to:

- a) The general effect of sleep deprivation among medical students.
- b) The main sleep complains among medical students.
- c) The factor of sleep deprivation among medical students. For example, up late studying, extra-curricular activities, video game addiction, and more.
- d) The effect of sleep deprivation among medical students. For example, weak immune system, short-term memory, unstable emotion, and more.

### **Sample**

Sample population were medical students from universities including UniSHAMS, UniSZA, UM,



UPM, UKM, UiTM and more.

### Study period

Research was done in a month, including discussion on how the research will be conducted, medical students on answering questions, data collection from questionnaires, getting result from SPSS, and report writing.

### Research tools and materials

Questionnaire:

Consist of 4 different section: Section A: Demographic detail, Section B: Sleep pattern, Section C: Sleep Behaviour, Section D: Effects of Sleep Deprivation.

### Data collection

Questionnaire through Google Form. Link of Google Form was sent through WhatsApp. In data analysis, Applied Chi-Square model and Pearson's Correlation to determine the association. All statistical analyses were conducted by using the Statistical Package for Social Science (SPSS) version 24.

## RESULTS

A total of 164 medical students (20.7% male and 79.3% female) were recruited in the study. The

demographic data is tabulated in Table 1. The age ranged from 19 to 26 years old with the majority of the participants being 20 years old (77.4%). Most of the participants were single (98.8%) as compared to the married participants (1.2%). Participants were varied from private and public universities in Malaysia. The results covering section B-D was shown in Table 2, 3 & 4.

For descriptive analysis, there is no relationship between sleep deprivation when coming to college and average hours of sleep. But there is a relationship and significant association between sleep-deprived when coming to college and academic performance hindered, and stress interferes ability to fall asleep.

No association was found between gender and sleep deprivation when coming to college.

Results of the Pearson correlation indicated that there was a significant positive association between the results scored on the Academic performance hindered and Stress interferes ability to fall asleep. Results of the Pearson correlation indicated that there was a significant weak negative correlation between the results scored on the sleep-deprived when coming to college and Stress interferes ability to fall asleep.

Table 1: Demographic data of participants (n=164).

Demographic detail	Frequency	Percentages (%)
Gender		
Male	34	20.7
Female	130	79.3
Marital status		
Single	162	98.8
Married	2	1.2
Age (years)		
19	3	1.8
20	127	77.4
21	17	10.4
22	8	4.9
24	3	1.8
25	2	1.2
26	4	2.4
University		
UM	8	4.9
UKM	6	3.7
UPM	8	4.9
UNIMAS	16	9.8
UITM	36	22.0
UIA	1	0.6
MSU	8	4.9
USIM	9	5.5
UNISHAMS	39	23.8
UNISZA	20	12.2
UNIKL	6	3.7
UNHAS	2	1.2
USM	5	3.0

Table 2. Sleep pattern analysis.

Characteristics	Frequency	Percentage (%)
<b>SLEEP DEPRIVED WHEN COMING TO COLLEGE</b>		
Yes	107	65.2
No	57	34.8
<b>SLEEP NEEDED TO FUNCTION WELL IN THE NEXT DAY (HOURS)</b>		
< 3 hours	2	1.2
4 - 6 hours	97	59.1
7 - 9 hours	61	37.2
> 9 hours	4	2.4
<b>HARD TO STAY AWAKE AND TO FOCUSED IN CLASS</b>		
Yes	143	87.2
No	21	12.8
<b>AVERAGE HOURS OF SLEEP (HOURS)</b>		
< 3 hours	11	6.7
4 - 6 hours	126	76.8
15.27 - 9 hours	25	15.2
> 9 hours	2	1.2
<b>LESS ENERGY AND MOTIVATION</b>		
Yes	46	28.0
No	3	1.8
Sometimes/depends	115	70.1
<b>NEGATIVE MOODS AND BEHAVIORAL CHANGES</b>		
Yes	126	76.8
No	38	23.2

## DISCUSSION

In this study, about 56.1% (92) of medical students did not experience insomnia while others, about 15.9% (26) students have difficulty sleeping due to mind disturbance when trying to sleep. This result was supported by a study mentioned that up to 60% of students suffer from poor sleep quality and 7.7% are having insomnia [6]. The hours of students sleep also lead to the quality to function well on the next day, based on the result of this study, 59.1% (97) students need 4 to 6 hours of sleep to function well and suffered from morning tiredness and only 1.2% of students need less than 3 hours. In another study, 31% of all students suffered from morning tiredness after having enough sleeping hours [7].

This study found a significant discrepancy between sleep deprivation and the effects on human functioning among medical students in terms of alertness and academic performance. The sleeping hours needed for a student to function well also interfere with the student ability to sleep through the night. Overall, the result in this research highlights more on the effect of sleep deprivation.

Sleep disturbances in undergraduate medical students are of particular interest because of the known relationship between sleep and mental health and the concern that the academic demands of medical training can cause significant stress [8]. Any additional undiagnosed sleep problem can presumably exacerbate mental

Table 3: Sleep Behaviour Analysis.

<b>Characteristic</b>	<b>Frequency</b>	<b>Percent (%)</b>
<b>Main Sleep Complaints</b>		
Trouble falling asleep	45	27.4
Trouble remaining sleep	34	20.7
Excessive sleepiness during the day	39	36.0
Snoring	7	4.3
Unwanted behaviours during sleep	19	11.6
<b>Breathing</b>		
I have been told that I snore loudly	10	6.1
I sweat a great deal at night	8	4.9
I sleep in normal breathing	121	73.8
I have been told that I stop breathing while asleep?	3	1.8
I have been told that I snore only when sleeping on my back	2	1.2
I awaken at night choking or gasping for air	2	1.2
I have trouble breathing when flat on my back	1	0.6
I have trouble breathing with my nose	7	4.3
I have morning headaches	10	6.1
<b>Parasomnias</b>		
I act on my dreams while asleep	14	8.5
I have frequent nightmares	19	11.6
I talk in my sleep	21	12.8
I have sleep walked as an adult	1	0.6
I did not experience parasomias at all	109	66.5
<b>Insomnia</b>		
I have trouble falling asleep	16	9.8
Thoughts start racing through my mind when I try to fall asleep	26	15.9
I have trouble remaining asleep	7	4.3
I awaken frequently during the night	14	8.5
I have difficulty returning to sleep if I awaken during the night	9	5.5
I did not experience insomnia	92	56.1

Table 4: Effect of sleep deprivation.

Characteristic	Frequency	Percent
<b>ACADEMIC PERFORMANCE HINDERED</b>		
Yes	21	12.8
No	38	23.2
Sometimes/depends	105	64.0
<b>OTHER FACTORS DEMINISH QUALITY AND QUANTITY OF SLEEP</b>		
Not tired at night, a "night owl"	12	7.3
Up late studying / doing homework	41	25.0
Out with friends / socializing	13	7.9
Involvement in extra-curricular activities (clubs/ work/sorority/team sports/etc.)	13	7.9
Uncomfortable sleeping environment	27	16.5
Usage of electronic devices before sleep (mobile phones/laptops/mp3/etc.)	31	18.9
Medical conditions (depression/sleep apnoea)	9	5.5
Video game addiction	7	4.3
I don't feel that my sleep quality/quantity is diminished	11	6.7
<b>STRESS INTERFERES ABILITY TO FALL ASLEEP</b>		
Not often (1 - 2 days a week)	109	66.5
Somewhat often (2 - 3 days a week)	34	20.7
Often (3 - 4 days a week)	17	10.4
Very often (at least 5 days a week)	4	2.4

stress in these students with potential long-term consequences for both individual's health and the overall performance of the health care system. Sleep disturbance could be either a cause, symptom or comorbidity with stress or with a psychiatric disorder [9]. Stress may cause many sleep difficulties, such as restless sleep, mid-sleep awakening and waking up too early. Medical students are subject to high levels of stress and work hard to increase and maintain their grade point average (GPA) at the expense of sleep [10].

This study also found that another factor that diminishes the quality and quantity of sleep is the usage of electronic devices before sleep with 18.9% about 31 medical students. A study in America found that 72% person bring cell phones into their bedroom and use them when trying to sleep and 28% person leave their phones before sleep [11]. Based on research done on medical students, 38.9% of the 36

students attending the same school schedule had a poor sleep quality according to the Pittsburgh Sleep Quality Index (PSQI) through the questionnaire [12]. A correlation between sleep onset, sleep irregularity and sleep length can be identified together with academic performance. Despite staying up for academic purposes, it disrupts the quality of sleep-wake cycle where it does not only increase fatigue and sleepiness but also worsens cognitive performance. This study is supported by recent research proving that poor quality of sleep is due to students afraid of missing out hence they are reported to assess technology use before sleep, technology use during sleep and social media use for both academic and non-academic purposes [13]. Students need to have a normal sleep cycle and this act can be done by researchers or higher authority to teach the students how to effectively manage sleep can improve their well-being.

Sleep deprivation will lead to a weak immune system by modifies various components of the immune system [14]. One of them is a decrease in cytokine levels. In a normal night-time sleeping habit, there will be an increase of cytokines and melatonin and decrease of cortisol. Cytokines affect the growth of all blood cells and other cells that help the body's immune and inflammation responses. They also help to boost anti-cancer activity by sending signals that can help make abnormal cells die and normal cells live longer.

Sleep deprivation has a great impact on the cardiovascular system. The sleep duration is an independent predictor for morbidity and mortality of the cardiovascular disease [15]. Cardiovascular disease is a non-communicable disease and is defined as a condition that involved narrowing or blocking blood vessels which may lead to heart attack, angina or stroke. According to Department of Statistic of Malaysia, cardiovascular diseases have been the leading cause of death in Malaysian since the early 1980s until today [16]. A few studies suggested that sleep deprivation has been related to a great risk of myocardial infarction and heart failure [17-18]. Sleep deprivation can also increase the sympathetic outflow to the heart or periphery through increasing catecholamine level, coronary vasomotor tone, blood pressure and heart rate, thus alter the balance between demand and supply of oxygen [19-20]. Hence, some studies rules out as blood pressure is significant to lead to hypertension that will deduce in high afterload pressure, exacerbating cell death and increase the risk to have cardiovascular disease [21-22].

Sleep deprivation was also found to be associated with mood deficit especially those that trigger an emotional response. Sleep was actually has a role in regulating emotional brain-states [23]. A study found out sleep deprivation associated with reduced functional connectivity between the amygdala and the medial prefrontal cortex (mPFC). A study found that reflecting sleep deprivation can induced disruption of top-down control of emotion as it was claimed to reduce prefrontal-amygdala functional connectivity [24]. Sleep deprivation can lead to serious changes in mood states and their regulation [25-27].

Sleep deprivation can also lead to obesity. Insufficient sleep is a possible cause of weight gain and obesity and have been researched by many scientific works of literature [28]. Sleep and obesity association has proved that insufficient sleep will increase the food intake during the night. In addition, short sleep duration, poor sleep quality, and late bedtimes are all associated with excess food intake, poor diet quality, and obesity in the modern obesogenic environment. Those people also not prefer to do some exercises during the day that increase the risk to become obese. A study found that fatigue and tiredness of sleep deprivation people, they tend to cut their physical activity and increase sedentary behaviour [29].

Sleep deprivation will increase the risk to have diabetes. Sleep duration of either 6 hours or less or 9 hours or more was associated with increased

prevalence of diabetes or glucose intolerance, compared with 7 to 8 hours of sleep per night, adjusted any confounders [30]. According to another study, sleep loss contributes to the development of insulin resistance and type 2 diabetes through multiple pathways, including a deleterious effect on glucose homeostasis, increased inflammation, and adversely affecting appetite regulation, leading to increased food intake, weight gain, and ultimately obesity [31].

In summary, research on the effect of sleep deprivation is significant because many people have different side effects of sleeping deprivation depending on their reasons. There has been much research and discussion conducted on these opinions of these community that are sleep deprived, including their factors, culture, sleep cycle behaviour resulting in conflicts with an impaired learning skill. Most of the research found was on the medical students and their components in academic performances.

## CONCLUSION

This results strongly support further investigation of the important aspect of medical students' life such as, sleep deprivation since coming to the university, sleep needed to function well, average hours of sleep per night and sleep behaviour and main sleep complaints. These could encompass the ability to concentrate as well as different aspects in learning and neuropsychological. In the future study, it is demanded to include more parameters. Biological marker such as cortisol level detection can be implemented as one of the tools of precise indicator of measurement sleep deprivation. Further investigation should focus and study also to other subgroups that have more psychological dysfunction, the nature of dysfunction and associated risk and protective factors. The improvement in the sleep variables may lead to sleep problems such as insomnia, parasomnia and breathing problem during sleep and a better life quality, which should be assessed in future studies.

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Review Article

EXERCISE AND OBESITY: ACTIVATION OF ANTIOXIDATIVE PATHWAY AGAINST OXIDATIVE STRESS

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ABSTRACT

Obesity is now acknowledged as a primary health burden which impact quality of life heavily due to its various complications. It is a chronic disease of multifactorial origin. Growing evidence proposes that one of the critical factors linking obesity with its associated complications is oxidative stress. Obesity induces systemic oxidative stress which causing the disordered production of adipokines that contributes to the metabolic syndrome development. They are more sensitive towards C-reactive protein (CRP) and other oxidative damage biomarkers. In contrast, the level of antioxidant defence markers is lower based on the total body fat as well as central obesity. One of the antioxidants is glutathione (GSH), which acts against free radicals and reactive oxygen species (ROS) in detoxification of xenobiotic compounds. Moreover, glutathione peroxidase (GPx), one of the most abundant in its family is the most effectual one against oxidant stress in erythrocytes and has some essential functions in phagocytic cells. Besides, it is also in charge of the removal of intracellular hydroperoxides. Therefore, this review attempts to evidence (i) the role of oxidative stress due to obesity as well as (ii) antioxidants as the potential opposition to this event as promising interventional therapy to manage obesity.

INTRODUCTION

Obesity: Incidence and Global Scenario

Based on World Health Organization (WHO) 2021, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016. The worldwide prevalence of obesity significantly increased between 1975 and 2016. In 2019, approximately 38.2 million children younger than 5 years were overweight or obese. Beforehand, it is viewed as a high-income country problem, however, overweight and obesity are escalating in low- and middle-income countries, particularly in urban settings. In Africa, since 2000, the number of overweight children under 5 has risen by almost 24%. Practically 50% of the children under 5 who were overweight or obese in 2019 lived in Asia. More than 340 million children and adolescents aged 5 -19 were overweight or obese in 2016 [1].

As stated by a systematic analysis of global data on the prevalence of overweight and obesity in adults [2], the prevalence of obesity in Malaysia (11.4% in males; 16.7% in females) was lower than that reported in Western countries, such as Australia (27.5% in males; 29.8% in females) and the United States (31.7% in males; 33.9% in females). Nonetheless, it was almost three to four times higher than in other Asian countries, such as India (3.7% in males; 4.2% in females), China (3.8% in males; 5.0% in females), Taiwan (4.3% in males; 6.4% in females) and Japan (4.5% in males; 3.3% in females).

Based on the statistic from World Population Review in 2019, Malaysia has the highest prevalence of obesity (15.6%) followed by Brunei (14.1%), Thailand (10%) and Indonesia (6.9%) [3]. According to the National Health and Morbidity Survey Malaysia (NHMS) in 2019 reported that 30.4% of overweight and 19.7% in adults, specifically high among women (54.7%). NMHS also revealed that 29.8% of children between 5-17 years old were overweight/obese [4]. On top of that, the health consequences of overweight and obesity are extensively associated with comorbidities and a high prevalence of cardiovascular diseases, diabetes, hypertension and several cancers [5]. This shows how supreme obesity is as one of the conditions that have a global impact with Malaysia is of no exception reinforcing the need to address it and manage it to the core.

Risk factor for obesity

Overweight and obesity are defined as an anomalous accumulation of excessive body fat [6] which may jeopardize health (WHO,2020). The World Health Organization (WHO) described overweight as a body mass index (BMI) of 25.0 to 29.9 kg/m<sup>2</sup> and obesity as a BMI of ≥30 kg/m<sup>2</sup> [7]. Obesity is a complex health issue that now has been considered as a disease. It results from an amalgam of individual factors and causes involving modifiable and non-modifiable factors. Habitual or

non-habitual behaviors which are all modifiable factors comprise inactivity, physical activity, medication use, dietary patterns, and other exposures. Other contributing factors are the food and physical activity environment, food marketing and promotion, as well as education and skills (CDC, 2020). On the other hand, hereditary factors such as genetics, family history, racial/ethnic differences are the non-modifiable factors that also play an important role in causing obesity. However, in general, obesity is undeniable to be greatly caused by those modifiable factors.

Over the years, the role of physical activity and diet remains the centre of attention in reducing the prevalence and risk of obesity worldwide. In order to maintain a healthy weight in the long run, observational cohorts evidently point out that "healthier" diets bring about better results. For instance, averaged 4-year weight gain throughout middle age is indicated by research in US health professionals as being closely linked to increased intake of sugar-sweetened beverages, processed and unprocessed red meats and potato chips and potatoes, but inversely linked to the intake of fruits, whole grain, vegetables, fruits, yoghurt and nuts [9]. Certain food groups like sugar-sweetened beverages, earn abundant attention as consumption of added sugar has been on the rise concurrently with prevalent obesity [10]. On a related point, Malaysia as a middle-income country is now experiencing rapid urbanisation and industrialisation which have brought significant changes to the dietary patterns and lifestyle of Malaysians [11]. At the same time, the introduction of modern fusion food has transformed the Malaysian diet from low calories of plant-based products to a diet rich in calories, fats and sugar [12].

Upper levels of physical activity correlate with both long-term weight maintenance after intentional weight loss and weight gain prevention. Among the vital findings in Nurse's Health Studies (NHS) II are that women who performed less physical activity (e.g., < 30 min/day) then increased it ( $\geq 30$  min/day) had remarkably reduced weight gain. Inversely, if physical activity is maintained at a low level, or fell from high to low, women had a higher risk of putting on weight [13]. Moreover, sedentariness has a hand in obesity; watching television and other sedentary activities at work or home escalated the risk of becoming obese [14].

Previous research revealed that Indians has the highest risk of being overweight and obese compared to other ethnicities which are suggestive of a role of genetics in obesity [15]. However, it does not rule out environmental factors like cultural influences and behavioural on food preparation and consumption [16]. Besides, the population with lower education levels had a higher prevalence of overweight as well as obesity. Unawareness to these people of good habits due to absence or little exposure to the right education subsequently prompt sedentary lifestyles, unhealthy eating, and impact them negatively in terms of chronic illness. Besides, obesity occurs similarly in the urban and rural areas which heavily suggests that it is not restricted to those loaded ones,

but is also widely spread to the rural due to rapid urbanization along with growing numbers of highly processed food advertising and food media in promoting fast food outlets and supermarkets [15] in contrast to the traditional home cooked-meals which contain healthy fibre with fruits and vegetables [17].

### **Obesity-induced oxidative stress**

Oxidative stress (OS) occurs due to an imbalance between the generation and degradation of reactive oxygen species (ROS) or reactive nitrogen species (RNS). They are partially reduced, oxygen-containing metabolites (some of them are free radicals) which are immensely reactive with the potential of oxidizing proteins, lipids and DNA. ROS are produced by mitochondria because of normal cellular metabolism and environmental factors but are exceptionally abundant in pathological conditions. Hydrogen peroxide ( $H_2O_2$ ), superoxide radicals ( $O_2^{\cdot-}$ ), singlet oxygen ( $^1O_2$ ) and hydroxyl radicals ( $\cdot OH$ ) are examples of ROS which are produced as metabolic by products [18]. However, proper ROS generation affects several processes like activation of transcriptional factors, protein phosphorylation, immunity, apoptosis and differentiation. Furthermore, they are involved directly and indirectly in immune-mediated defence mechanisms against pathogenic microorganisms [19].

Obesity is found to be related to low-grade chronic systemic inflammation that occurs in adipose tissues. Activation of the innate immune system influence this condition by promoting pro-inflammatory responses while a systemic acute-phase response triggered by OS takes place. Adipose tissue, and endocrine and storage organ which is essential for homeostatic control of energy balance, is predominantly composed of adipocytes. It secretes hormones and cytokines (adipokines or adipocytokines) which act for paracrine, endocrine and autocrine action. However, in obese people, the adipocytes limit the normal functioning level thus unable to function properly as an energy storage organ. The excessive adipose tissue also has been recognized as a source of pro-inflammatory cytokines including interleukin (IL) - $1\beta$ , IL-6 and tumour necrosis factor-alpha (TNF- $\alpha$ ) [20], which are the most prominent mediators involved during the early inflammatory response. In addition, it results in fat being inappropriately accumulated in important organs; heart, liver, pancreas which can cause the dysfunction of this organ. In physiological and hazardously in pathological conditions, adipokines (MCP-1,-2,-4 along with MIP -1a, -1b,-2a) trigger infiltration of macrophage and subsequent excess production of ROS and inflammatory cytokines, give rise to OS and, eventually, a major, erratic production of other adipokines [21, 22] ROS itself also induces the release of pro-inflammatory cytokines and expression of growth factors (e.g., insulin-like growth factor-1 (IGF-I) and connective tissue growth factor,) and adhesion molecules [23] through redox-sensitive transcription factors, specifically the NADPH oxidase (NOX) and NF- $\kappa$ B pathway [24].



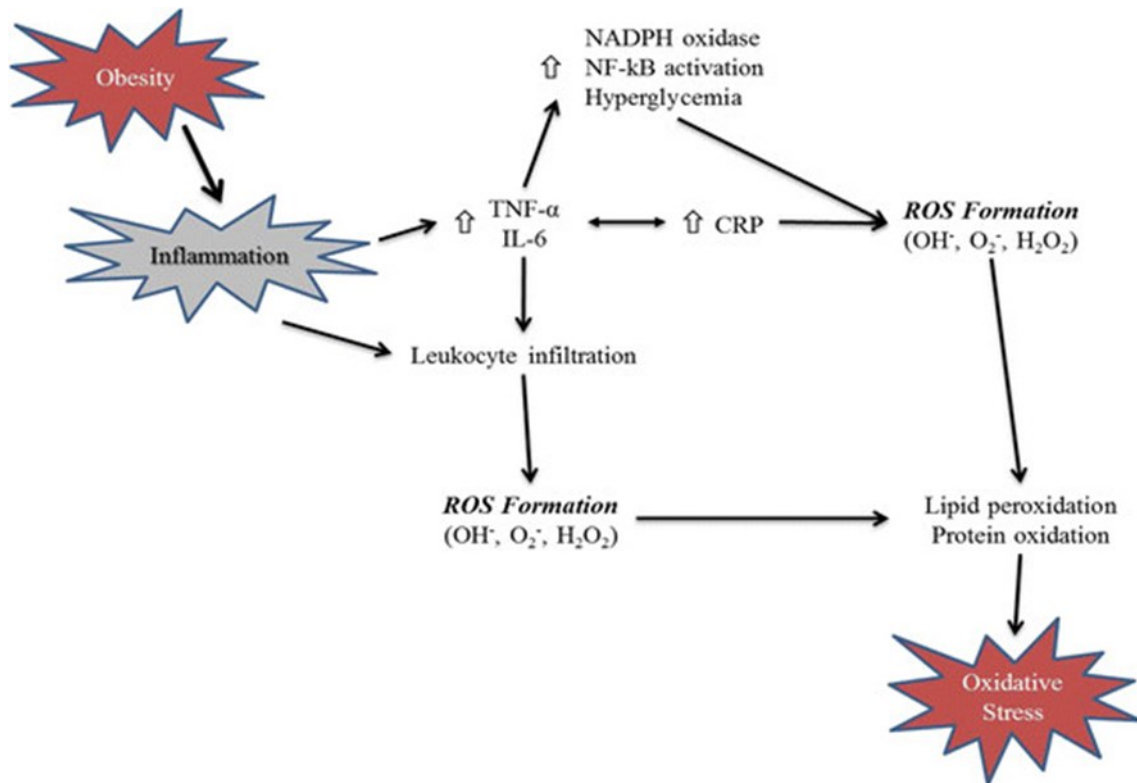


Figure 1. The illustration summarizes the obesity-induced oxidative stress in general, in which obesity is proven to cause inflammation thus bringing about a series of pathways involving pro-inflammatory cytokines and increased production of reactive oxygen species (ROS) which end up with oxidative stress [25].

At the same time, impairment of the activity of nuclear factor E2-related factor 2 (Nrf2) occurs. This results in an impediment of the expression of Nrf2 downstream targets (antioxidant and phase II detoxifying enzymes) leading to debilitated body antioxidant defences [26]. In addition, antioxidant sources are depleted including glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT), vitamin A, vitamin E,  $\beta$ -carotene and vitamin C [27]. The latter is through modulation of expression of sodium-dependent vitamin C transporters believed to be caused by metabolic and/or OS, thus adversely affecting cellular uptake and in the bigger picture, vitamin C homeostasis. All of these contribute to greater susceptibility to oxidative damage in obese subjects [28].

Obesity correlates highly with hyperglycemia and insulin resistance. Overabundant intracellular glucose escalates the tricarboxylic acid cycle and the glycolytic pathway which leads to the overproduction of nicotinamide adenine dinucleotide hydride (NADH) and flavin adenine dinucleotide hydride (FADH<sub>2</sub>). It results in increasing proton gradient across the mitochondrial inner membrane which further causes leakage of an electron at complex III, leading to the formation of superoxide. Glyceraldehyde-3-phosphate dehydrogenase is inhibited by these free radicals thereby diverting upstream metabolites into four alternative pathways [29]: (1) shifting of glucose to the polyol pathway; (2) shifting of fructose-6-phosphate to the hexosamine pathway; (3) production of methylglyoxal, the vital precursor of advanced

glycation end products (AGE) by triose phosphates; and (4) conversion of dihydroxyacetone phosphate to diacylglycerol which activates the Protein Kinase C (PKC) pathway. Activation of all these pathways generate oxidative stress either by; impairing antioxidant defences or amplifying the production of free radical. Moreover, polyol pathway activation causes depletion of nicotinamide adenine dinucleotide phosphate hydride (NADPH) as well as enhancement of glucose conversion to sorbitol which is responsible for activation of various stress genes causing oxidative stress [30].

Another well-known point is hyperleptinemia. Leptin, one of the adipocyte-derived factors, is positively associated with obesity, showing that it plays a part in obesity-induced oxidative stress [31]. Leptin activates nitrogen oxides (NOX) and induces the production of reactive intermediates like hydroxyl radical and H<sub>2</sub>O<sub>2</sub> [32]. Secondly, hyperleptinemia also escalates the process of oxidation of mitochondrial and peroxisomal fatty acid, with consequential stimulation of ROS production via the mitochondrial respiratory chain [33]. It also triggers the proliferation of monocytes as well as macrophages thus promoting the production of proinflammatory cytokines which fortify OS [34]. Increased C-reactive protein (CRP) levels are also reported during the administration of leptin, further verifying inflammatory effects. As per these data, during weight loss, there is a reduction of obesity-associated inflammatory

markers and circulating leptin levels (Figure 1) [35].

In obese subjects, accumulation of excessive fat leads to a pathological rise of serum-free fatty acids (FFA) levels sequentially impairs glucose metabolism [36], favours adipose, muscular and hepatic accumulation of energy substrates; fats and glucose [37] and elevates higher mitochondrial and peroxisomal oxidation. This gives rise to significant synthesis of free radicals, depletion of adenosine triphosphate (ATP), mitochondrial DNA injury, OS [38] and, in the end, lipotoxicity. Besides, upbuilding of free radicals is majorly involved in vascular endothelium damaging, triggering endothelial dysfunction (ED) and development of cardiovascular complications related to obesity. Notoriously, cardiovascular events determine high premature mortality rates of obese patients (Figure 2).

### CONCEPT OF ANTIOXIDATIVE PATHWAY

#### Activation of the antioxidative pathway

As overproduction of reactive oxidants is harmful, they are balanced out by complex antioxidant defence systems regulated by a series of pathways which is the Kelch-like ECH-associated protein 1 (Keap1) - nuclear factor erythroid 2-related factor 2 (Nrf2) - antioxidant response elements (ARE) pathway which occurs on a day-to-day basis to maintain the homeostasis in general by regulating the transcription of numerous detoxification genes and antioxidant genes. Under normal physiological conditions, bonding of Nrf2 with its negative regulator Keap1 (Kelch-like ECH

-associated protein 1), which is a redox regulator substrate adaptor for the Cullin (Cul)3-RING-box protein (Rbx)1 ubiquitin ligase causes Nrf2 to remain idle as it directs Nrf2 to be sequestered in cytosol by ubiquitination [39]. Keap1, a cysteine-rich protein is oxidized by ROS, consequentially, altering its conformational state, freeing Nrf2 [39] [40]. Thus, increasing OS encourages the dissociation of Nrf2 from Keap1, which activates a series of pathways to occur from initially bring about to Nrf2 translocation in the nucleus for it to heterodimerize with musculoaponeurotic fibrosarcoma proteins (MAF proteins), to bond with a specific DNA sequence known as the antioxidant response element (ARE, 5'-TGACNNNGC -3') [41]. This results in the activation of a large number of genes associated with the production of antioxidative and cytoprotective proteins including NADPH dehydrogenase, quinone 1 (NQO1), heme oxygenase-1 (HO-1), glutathione S-transferase (GST), c-glutamylcysteine synthetase, superoxide dismutase (SOD) glutathione peroxidase 1(GPx-1) and glutathione reductase (GR) (Figure 3) [42].

#### How antioxidative pathways act on obesity-induced oxidative stress

In accordance with the increasing prevalence of obesity, governmental and non-governmental organizations recommend a broad range of strategies to combat it. For instance, various health programs had been initiated by the Malaysian Government such as 'My Weight My Health', 'Mysihat' and 'Eat Right, Move Right:

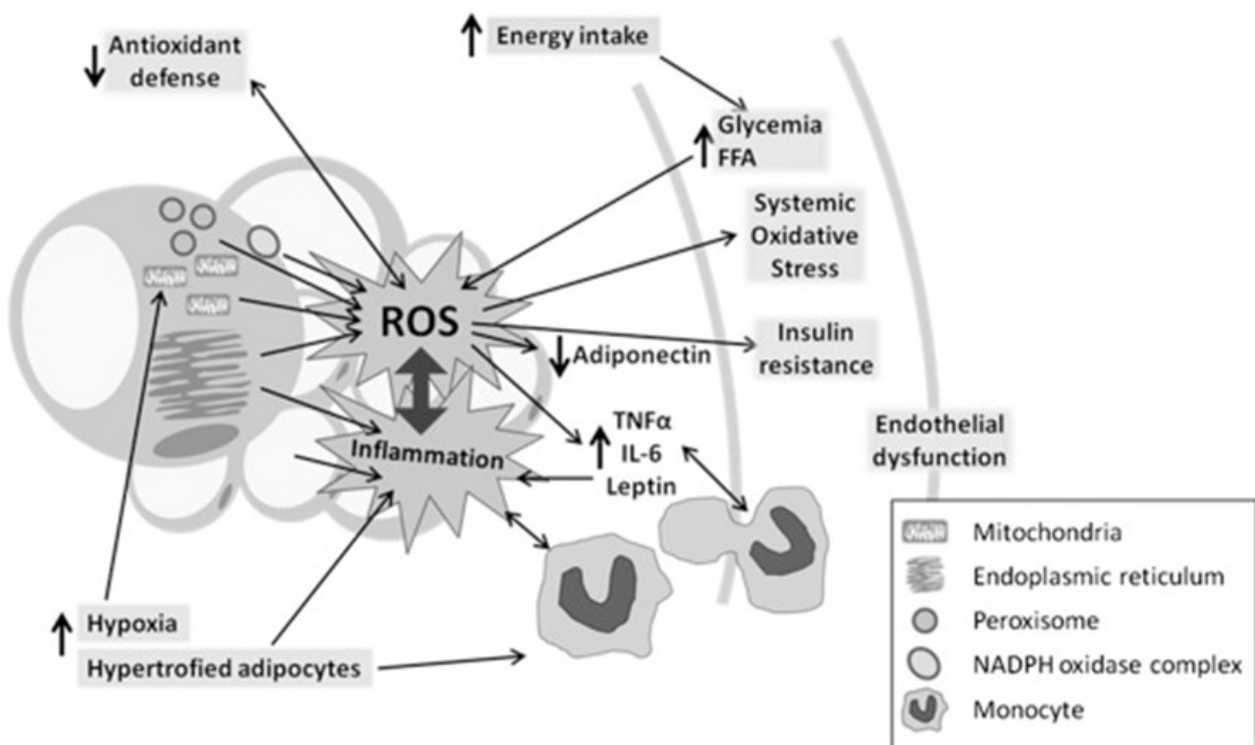


Figure 2: Illustration depicts how obesity induces oxidative stress at subcellular levels, by excessive production of ROS and reduced antioxidant defence through several mechanisms [38].

Fight Obesity to promote a healthy lifestyle among Malaysian citizens by disseminating information regarding proper dietary practices, nutrition and fitness through physical activities or exercises [43]. This is important in order to curb morbidity and mortality rates as well as health care expenses. A study by [43] exhibited that there was a significant additional increase in medical expenditure due to obesity and the actual cost that a patient should pay is very less due to being heavily subsidised by the Malaysian government. At present, emerging studies are aiming in modulating redox homeostasis as tools to forestall or slow down the progression of obesity-associated pathologies. Antioxidants are being looked into keenly as a possible option in controlling obesity and its associated complications.

In short, obesity-induced oxidative stress is briefly by several mechanisms; dysfunction adipose tissue, hyperglycemia, hyperleptinemia and hyperlipidemia resulting in oxidative stress due to an imbalance between ROS generation and its detoxification by antioxidant systems, in favour of the former. On the other side, antioxidants nullify the effect of highly reactive ROS by converting them into less reactive species and eliminating the byproducts through various reactions, preserving cells from oxidative damage, which will be discussed in many details.

Antioxidants can be classed into enzymatic and non-enzymatic types, in which the latter, its exogenous form is found mainly in the diet. Besides the other beneficial reactions through modulations of Keap1-Nrf2 signalling axis in response to ROS, the antioxidant enzymes produced during the pathway also play

their role in the antioxidant defence system. They are effective in deactivating or stabilizing free radicals before the free radicals attack cellular components. These enzymatic antioxidants function by giving up part of their electrons to make the free radicals stable or by reducing their energy. Innumerable studies have been focused on the advantageous effects of antioxidant enzymes. Among the popular enzymatic antioxidants are catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD). However, they also work interactively and synergistically with non-enzymatic ones in order to perform their function [44].

### Catalase (CAT)

CAT is well known for its key role in controlling  $H_2O_2$  concentration and other cytotoxic oxygen derivatives. It acts by breaking down two hydrogen peroxide molecules into one oxygen molecule and two water molecules in a two-step reaction. Basically, the first step of the reaction mechanism involves a high spin ferric ( $Fe^{III}$ ) state that reacts with peroxide molecules to form compound I intermediate, a porphyrin  $\pi$ -cation radical containing  $Fe^{IV}$ .  $H_2O_2$  removes one of the protons from one end of the molecule and place it at the other end. The transferring of the proton is via histidine residue in the active site. This action polarizes and breaks the O-O bond in hydrogen peroxide. Secondly, the regeneration of enzymes by  $H_2O_2$  which is used as a reductant produces oxygen and water. The native resting-state  $Fe(III)$  is formed by oxidation of an electron donor (here second  $H_2O_2$ ) in compound I, a highly-oxidizing  $Fe(IV)$  species (Figure 4) [45].

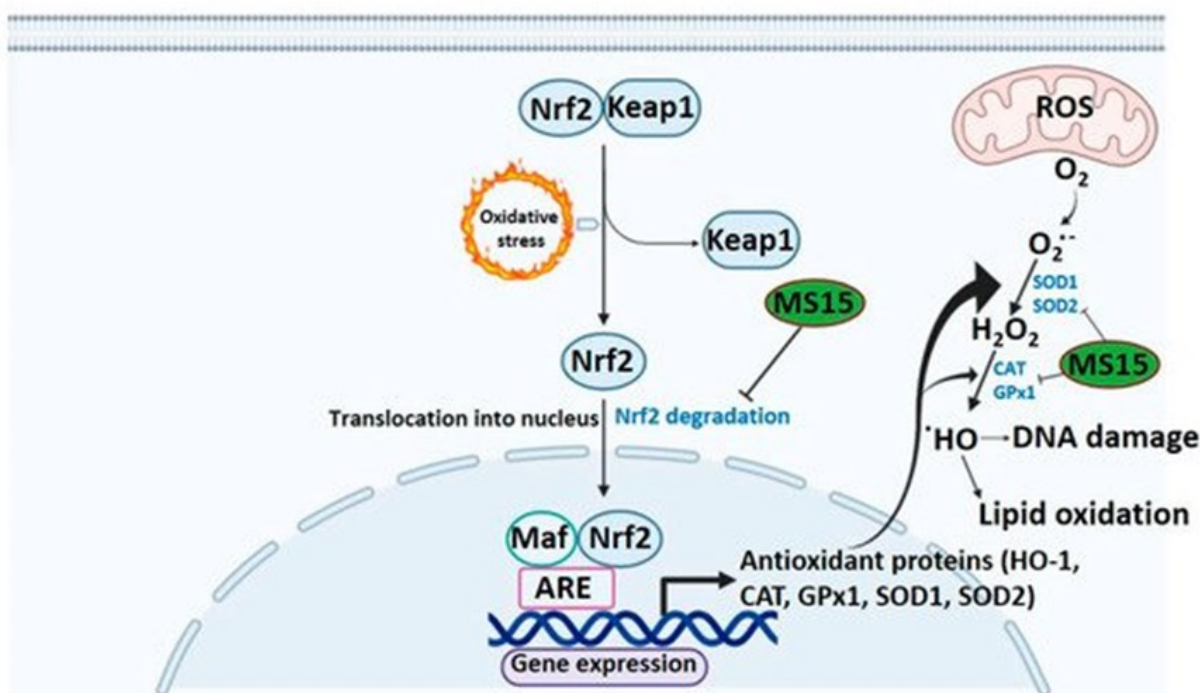


Figure 3: The activation of the antioxidative pathway mediated by oxidative stress causing abnormality to Keap1 configuration causing activation of Nrf2 pathway. This lead to the production of enzymatic antioxidants which play the role to reduced free radicals before they cause damage to cells particularly to protein, lipid or DNA [47].

### Glutathione peroxidase (GPx)

Secondly, GPx, an enzyme-containing four selenium-cofactors catalyses the formation of oxidized glutathione (GSSG) from glutathione (GSH) by creating a disulfide bridge with another glutathione molecule while detoxifying these molecules by reacting with hydrogen peroxides or lipid peroxidation [46]. It is partly responsible for hydroperoxides reduction. The involvement of GPx in the detoxification of xenobiotics showed that this antioxidant enzyme provides the most important defence against the peroxidative damage of biological membranes in the mammalian cell (Figure 5) [47].

### Superoxide dismutase (SOD)

The third one is SOD, which contains metal ion co-factors, that, depending on the isozyme, can be of various elements such as zinc, copper, iron or manganese. The role of these cofactors is to donate an electron to ROS and regenerate throughout the

catalytic mechanism where SOD acts as the initial defence against reactive oxygen species (ROS)-mediated injury [48]. Furthermore, it catalyzes the dismutation of superoxide anion free radical ( $O_2^{\bullet-}$ ) into molecular  $H_2O_2$  and oxygen. This reaction is followed by alternate oxidation-reduction of metal ions present in the active site of SODs (Figure 6) [49].

Apart from these enzymatic antioxidants, non-enzymatic antioxidants like lipoic acid also takes a lead. Being classed as "thiol" or "biothiol", these sulphur-containing molecules catalyze the oxidative decarboxylation of alpha-keto acids, for example,  $\alpha$ -ketoglutarate and pyruvate in Krebs cycle [50]. Lipoic acid and dihydrolipoic acid (DHLA), its reduced form, counteract the free radicals in both aqueous and lipid domains, hence, the nickname "universal antioxidant" [51]

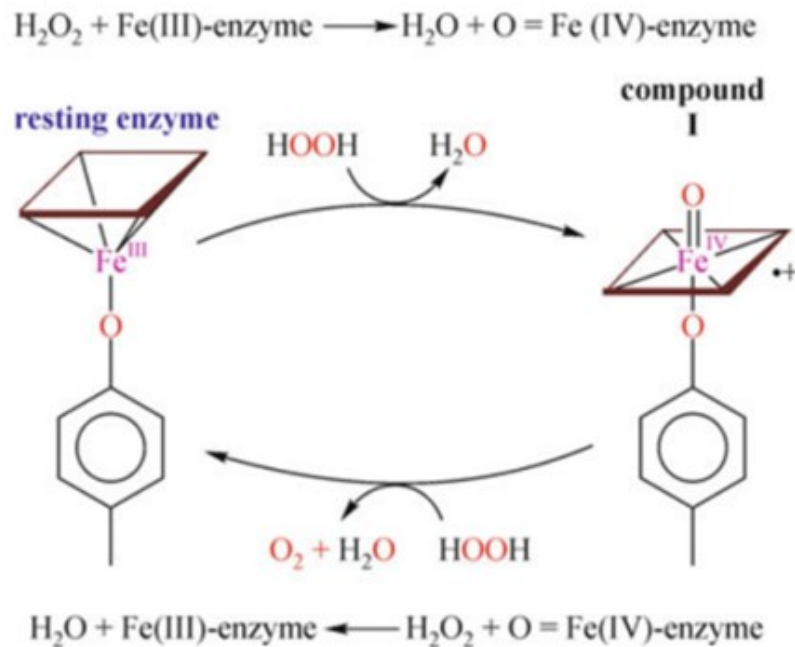


Figure 4 : Two-stage mechanism of catalase action [45].

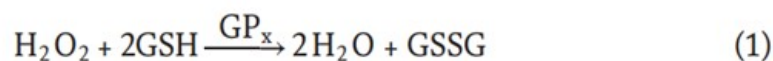


Figure 5: Glutathione oxidation process [48].



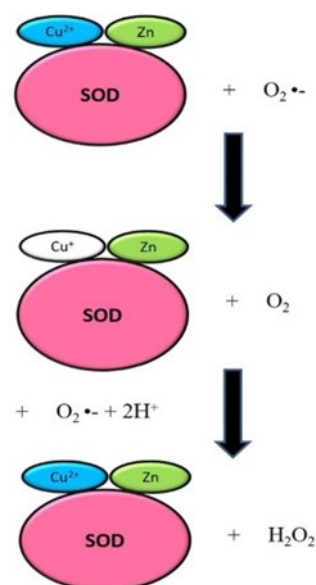
Additionally, the exogenous ones such as dietary micronutrients also take part in the antioxidant defence system. These include b-carotene, Vitamins C (ascorbic acid) and Vitamin E (tocopherols and tocotrienols). Vitamin E can protect against lipid peroxidation and stabilize biological membranes [52]. Vitamin C operates as a free radical scavenger in the aqueous phase of cytoplasm and can regenerate reduced tocopherol [53]. On the other hand, Vitamin E and b-carotene act as antioxidants in the lipid environment. In one study, cotreatment with vitamins C and E demonstrated a synergistic antioxidant effect [54]. Other important elements include selenium, copper, zinc and manganese since they serve as cofactors for enzymatic antioxidants.

Thus, it becomes much clearer that antioxidants are beneficial in tackling obesity which opens up to different discussions on how to enhance antioxidants outweighing its reduced level in obesity-induced OS. To no surprise, lifestyle modifications; exercise/physical activities, weight reduction and a balanced natural diet are proven to have an advantageous effect on antioxidant levels.

#### Exercise stimulates an antioxidative pathway

It is found that during physical exercise, the energy requirement of the muscular system rises the oxygen consumption to a level 10–20 times above that of the [53]; this prompts the escalation of ROS flow in the muscle fibres [54]. Skeletal muscle is the chief ROS manufacturer during exercise, and the cellular sites of abundant production comprising the mitochondria, xanthine oxidase, phospholipase A2, (NADPH) oxidase, and some immune-system cells, such as neutrophils, eosinophils, monocytes and macrophages [55]. In addition, increased body temperature and decreased blood pH due to the presence of lactic acid has been reported to speed up the production of ROS, increasing OS [56]. Nonetheless, during physical training, in response to the abundance of ROS, peculiarly when it is not exhaustive, activation of the enzymatic Endogenous Antioxidant System (EAS) is stimulated, which modulates enzymes such as GR, CAT and GPx along with the non-enzymatic EAS, including alpha lipoic acid, glutathione, and so forth.

Based on a cross-sectional study conducted on overweight/obese postmenopausal women of age 45–64, an active lifestyle (aerobic exercise for at least 30 minutes, three times per week) was linked to enhanced antioxidant enzyme activities, particularly, CAT and SOD, in peripheral blood mononuclear cells [57]. Acute training and chronic training were proven to have different responses to OS. Moderate regular training is postulated to induce EAS, protect the body from OS-induced damage and reduce the probability of cardiovascular diseases as well as death. Conversely, acute exhaustive training has been observed to markedly increase free radical production [58]. It is demonstrated that occasionally, sedentary individuals with preceding cardiovascular disease have sudden cardiac death due to vigorous exercise, though, not in the case with moderate exercise as accustomed practice [59]. Therefore, regular exercise does act as an anti-inflammatory



**Figure 6:** The general catalytic mechanism for dismutation of O<sub>2</sub> by Cu-ZnSOD [50].

strategy and a natural antioxidant in combating obesity and its associated complications, whilst, it is also necessary to take into account the intensity, modality and duration of training along with individuals' clinical antecedents.

Besides, weight reduction is shown to escalate the antioxidants level. It is known that weight reduction increases antioxidant defences, diminishes oxidation markers and improves cardiovascular and metabolic risks associated with human obesity [60]. A study by Hermsdorff et al (2011) that the values of antioxidants in plasma increases considerably as a result of replacing balloons in the stomach of obese people for six months as well as the reduction in the BMI and weight [61]. This study also confirmed the effect of weight loss with the enhanced antioxidants capacity. Another study by Del Rio et al. (2011) proved that with dietary intervention and 10% of weight loss, the correlation of enzymatic antioxidants and their synergistic action to eliminate free radicals had increased especially glutathione peroxidase which is the focus of this study [62]. In a study by Stephenie et al. (2020), a 10% reduction in weight resulted in increased Vitamin D concentrations in previously vitamin D-insufficient obese individuals [63]. Besides, obesity was an independent risk factor in draining protective enzymes in erythrocytes; individuals with normal BMI had higher SOD and GPX activities in comparison with obese people [64]. Therefore, weight loss can bring about an increase in antioxidant enzymes activities. In a study conducted by Mattmiller et al. (2013), a 10% reduction in weight resulted in increased Vitamin D concentrations in previously vitamin D-insufficient

obese individuals [64]. Besides, obesity was an independent risk factor in draining protective enzymes in erythrocytes; individuals with normal BMI had higher SOD and GPX activities in comparison with obese people [65]. Therefore, weight loss can bring about an increase in antioxidant enzymes activities.

## CONCLUSION

Obesity is a worrying prevalence which spiked up in numbers not only in developed countries but also in underdeveloped countries resulting from main changes in dietary pattern and lifestyle such as sedentary lifestyle, lack of exercise or physical inactivity as well as increasing numbers of fast-food chain and highly processed food while metabolic and genetic studies disclose that there are individuals who are more liable to gain weight compared to others. Obesity induces oxidative stress through several mechanisms; excessive and dysfunction adipose tissue, hyperglycemia, hyperleptinemia, and hyperlipidemia which all has been described to escalate ROS-generation systems and to reduce its detoxification by antioxidant systems, in favour of the former. In accordance with this issue, the Malaysian Government had started various health programs such as 'My Weight My Health', 'Mysihat' and 'Eat Right, Move Right: Fight Obesity to promote a healthy lifestyle among Malaysian citizens by disseminating information regarding proper dietary practices, nutrition and fitness through physical activities or exercises. One of the rising subjects which garnered much attention recently is antioxidants. The activation of antioxidants in obesity-induced oxidative stress is being keenly analyzed as a possible option in combating obesity and its associated complication. At the moment, modification of lifestyle including increased physical activity, weight reduction and practice of healthy diet especially ones rich in antioxidants, including vegetables, fruits and balanced micronutrients, have been proposed as beneficial strategies as they are all proven to have linked in increasing antioxidants level.

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## Case Report

### ANTIMALARIA AND BULL IN THE EYE

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systemic lupus erythematosus;  
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chloroquine;  
maculopathy;  
Bull's eye

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#### ABSTRACT

*Hydroxychloroquine (HCQ) and chloroquine (CQ) are antimalaria medications that have been widely accepted and used to treat systemic lupus erythematosus (SLE). It has been improving the outcome and increase life expectancy. However, long-term intake of HCQ/CQ or at high dose of these medications may cause irreversible ocular toxicity. In the eyes, it can manifest as maculopathy and keratopathy. The damage done will continue to progress even years after stopping the medication. Early detection and stopping the medication is recommended in order to limit the potential blinding complication especially in young SLE patient.*

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#### INTRODUCTION

Chloroquine (CQ) was initially developed as an anti-malaria medication. Later, it was found that it is beneficial in the treatment of rheumatological conditions such as rheumatoid arthritis and systemic lupus erythematosus (SLE) [1,2]. Among the side effect that is caused by this antimalarial drug is retinopathy. It is irreversible despite stopping the drug. We present a case of Bull's eye maculopathy in a young SLE patient that received CQ therapy.

#### CASE PRESENTATION

A 38-year-old Malay lady was diagnosed with SLE for the past 17 years. She was first diagnosed at the age of 15. She first presented with chronic multiple joints pain, facial rash, and alopecia. She was then started on CQ 250 mg daily together with oral prednisolone. The ocular screening was performed within the first month of starting CQ treatment. Her vision was 6/6 in both eyes. The ocular assessment was normal with no retinopathy and normal optic nerve function test.

She was on regular CQ and oral prednisolone treatment. Her compliance was good. She had yearly ocular review. After 7 years of therapy, both medications were discontinued in view of stable SLE. A year later, she was restarted on hydroxychloroquine (HCQ) 200 mg together with oral prednisolone 30 mg daily due to relapse of SLE with recurrence of joint pain and facial rash. Yearly fundus assessment was normal with 6/6 vision bilaterally.

Six years after HCQ therapy, both fundi showed parafoveal hypopigmented lesion at macular area (Figure 1). She was otherwise asymptomatic and her visual acuity remained 6/6 in both eyes. There was deficit of Ishihara pseudoisochromatic color plate test bilaterally which was worst on the right eye. Optical coherence tomography (OCT) showed normal central macular thickness bilaterally with bilateral parafoveal thinning evidenced by loss of the foveal contour giving the shape of flying saucer. Hypopigmented lesion surrounding the fovea correspond to the loss of outer segment of photoreceptor and retinal pigment epithelium (RPE)

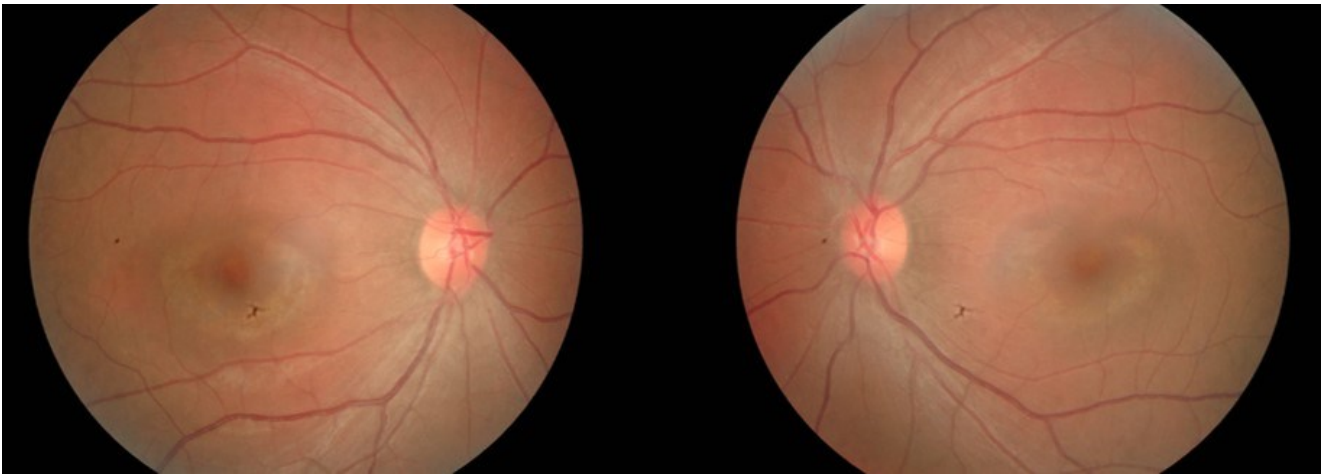


Figure 1: Bilateral parafoveal hypopigmented lesion surrounding the fovea at 6 years of hydroxychloroquine therapy (RE: right eye, LE: left eye).

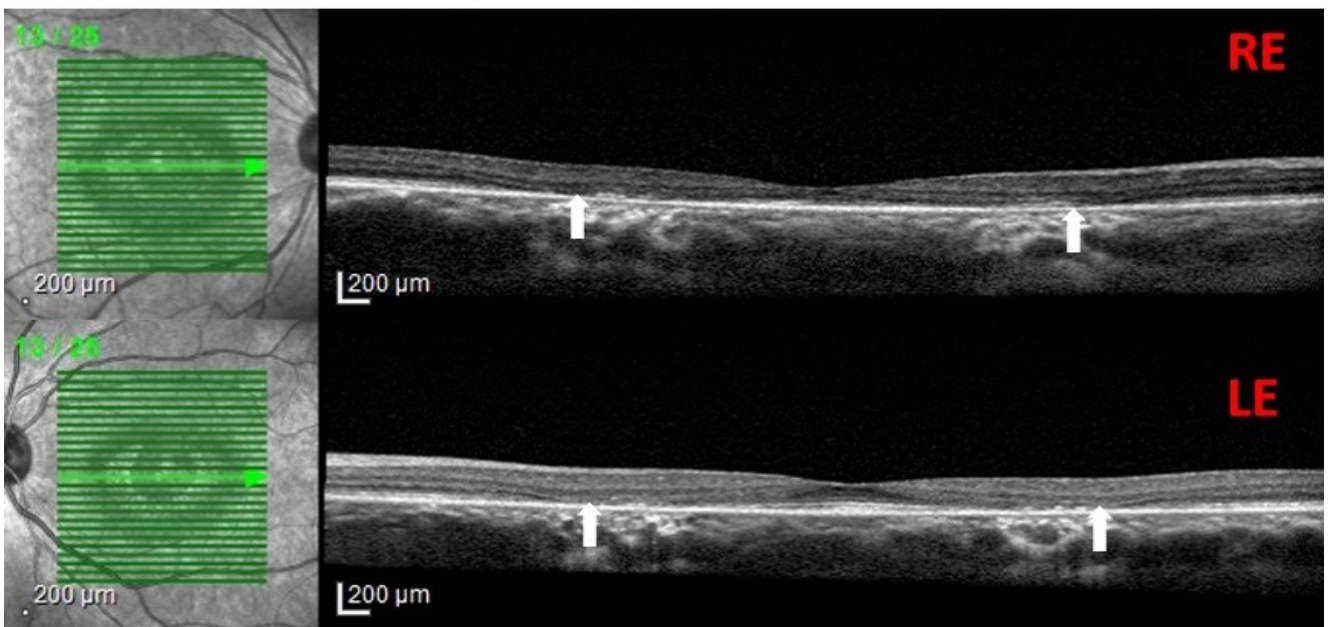


Figure 2: Optical coherence tomography of macula at 6 years of hydroxychloroquine therapy showing parafoveal thinning on both eyes (RE: right eye, LE: left eye) evidenced by loss of the foveal contour giving the shape of flying saucer. Hypopigmented lesion surrounding the fovea corresponds to the loss of the outer segment of photoreceptor and retinal pigment epithelium (arrow).

(Figure 2). In view of bilateral maculopathy HCG therapy was stopped. However, the oral prednisolone was continued with tapering dose and azathioprine (AZA) 50 mg daily was added.

Her vision continued to deteriorate over time despite stopping the HCQ medication. Review at 5 year after stopping HCQ therapy, her best corrected visual acuity (BCVA) was 6/60 and 6/7.5 in the right and left eye respectively. Fundus examination showed complete RPE depigmentation ring on the right macula and incomplete hypopigmented (RPE depigmentation) ring in the left macula (Figure 3). Central macular thickness by OCT was 173  $\mu$ m in the

right eye and while the left macular thickness was 215  $\mu$ m. The parafoveal thinning was more pronounced in the right eye (Figure 4). Visual field was performed in this patient; however, the finding was not reliable.

Her current medication includes AZA 50 mg daily and oral prednisolone 10 mg daily. She is currently well with BCVA stable at 6/45 and 6/7.5 in right and left eye. Her natural lens is clear and intra-ocular pressure (IOP) is within normal range despite prolong usage of oral corticosteroid. She remains on yearly ocular assessment to closely monitor the progression of HCQ maculopathy.

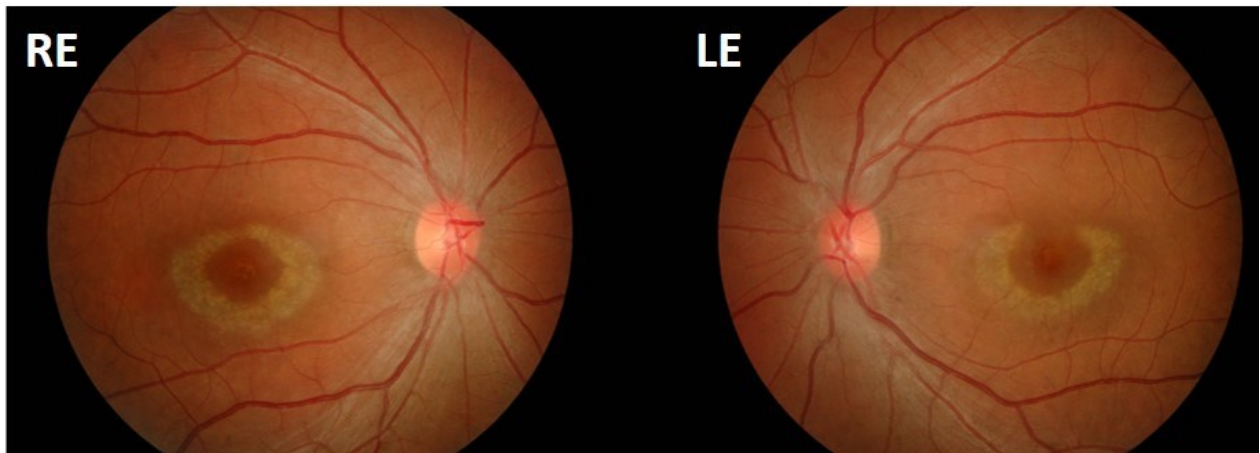


Figure 3: Funduscopy finding 5 years after discontinuation of hydroxychloroquine therapy showing worsening parafoveal hypopigmented (retinal pigment epithelium depigmentation) ring on both eyes (RE: right eye, LE: left eye).

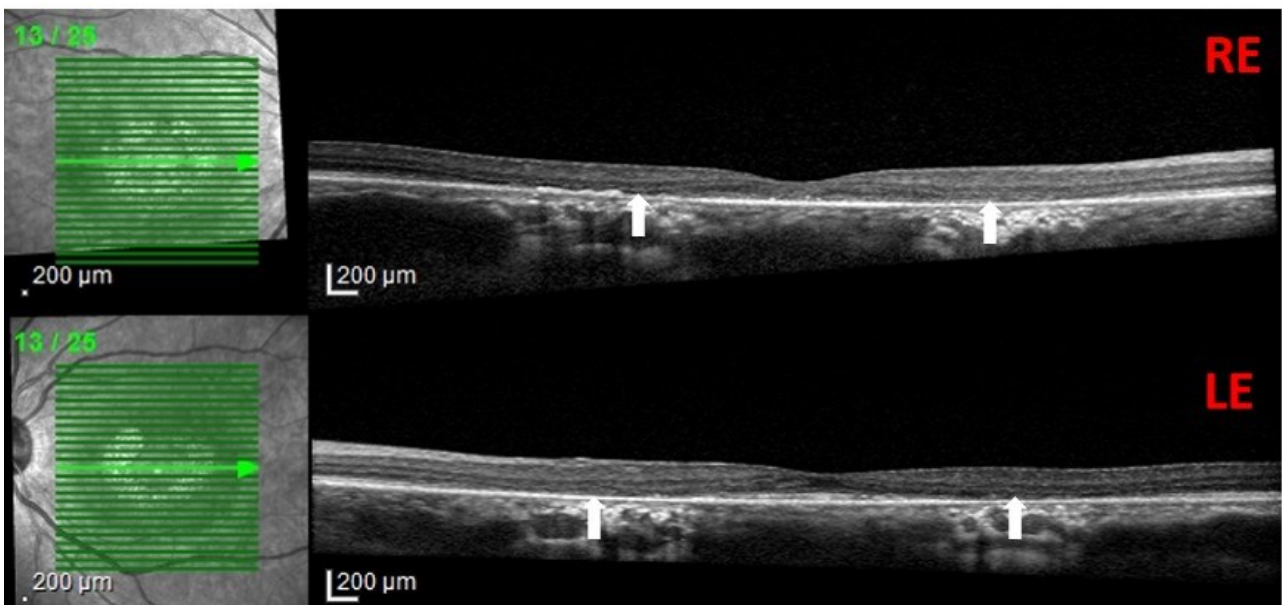


Figure 4: Optical coherence tomography of macula after 5 years discontinuation of hydroxychloroquine therapy showing worsening of parafoveal thinning (arrow) in both eyes (RE: right eye, LE: left eye), more pronounced temporally in the right eye.

## DISCUSSIONS

Systemic Lupus Erythematosus is a chronic systemic autoimmune disease affecting multiple organs thus the variable presentation, course and prognosis. It is characterized by remissions and flares [3]. It affects ocular structure from anterior to posterior segment, either partly or the whole ocular system. Damages to the ocular system could be due to the effect of the disease or due to the treatment of the SLE [4,5].

Drug induced maculopathy in SLE is usually cause by treatment with antimalarial drugs; CQ or HCQ. Patient that received more than 6.5 mg/kg/day of HCQ and 3 mg/kg/day of CQ have high risk of maculopathy based on ideal weight [6]. In recent

publication it is recommended to screen patient receiving more than 5 mg/kg/day and 2.3 mg/kg/day of real body weight [5].

Mechanism of CQ and HCQ toxicity is not well understood. It is thought that the accumulation in retina by binding to the melanin in RPE which cause the prolong effect locally [5]. Beside the dose and duration of the drugs, other risk factors that contribute to the toxicity are underlying macular diseases, concurrent renal disease which is common in SLE patients, and concurrent treatment with tamoxifen [5].

Currently the only management of CQ and HCQ retinopathy is cessation of the drugs. Stopping of the

drugs does not prevent or halt the progression of retinopathy [5]. Hence, there is the need to screen and monitor for the drugs induced retinopathy. The decision to stop medication in a patient needs to be discussed with the physician who is managing the patient, and another drug should be considered [5].

The recommendation by The Royal College of Ophthalmologists is to screen the patients receiving CQ or HCQ 5 years after the baseline at the time of starting the medication. Patient who have severe risk factors such as renal impairment (eGFR less than 60ml/min/1.73m<sup>2</sup>), Tamoxifen use, high doses of CQ (> 2.3 mg/kg) or HCQ (> 5.0 mg/kg) need to be assessed yearly [7].

Automated visual fields and spectral-domain OCT (SD-OCT) are recommended for primary screening. Spectral-domain OCT is an objective screening to look for any changes in the retinal layer. Early finding in OCT includes thinning of photoreceptor layer, ellipsoid layer, outer nuclear layer and RPE. Most commonly seen are changes in the parafoveal area, however in Asian eyes changes are most commonly seen in more peripheral retina [8].

Automated visual field test is helpful when used together with other investigation in early detection of CQ retinopathy [5,8,9]. It shows changes in the macula with 10-2 testing. But for Asian patient wider test (24-2 or 30-2) are recommended as maculopathy tends to affect the more peripheral extramacular area.

Other additional screening tests are multifocal electroretinogram (mfERG) that can provide objective confirmation of visual field loss. Fundus autofluorescence may reveal early parafoveal or extramacular photoreceptor damage, demonstrated as area of increase autofluorescence. Later, in advanced stage it will show hypo-autofluorescence which indicate RPE death [8,9].

## CONCLUSION

In conclusion screening of retinopathy in SLE patients receiving CQ or HCQ is important as the damage are irreversible [8,9]. Even with cessation of medication, the CQ or HCQ maculopathy can still progress. Early and timely detection is crucial in order to stop the medication as soon as possible. Maculopathy causes deterioration of visual acuity, leading to decrease in quality of life.

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## Case Report

### DEVIL IN DISGUISE: BASOSQUAMOUS CARCINOMA OF EYELID

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#### ABSTRACT

*Basosquamous carcinoma is a rare epithelial malignancy of the eyelid with aggressive and destructive behaviour. They share the features of both squamous cell and basal cell carcinoma. We report a case of a patient who presented with left lower lid enlarging mole and clinical signs of basal cell carcinoma. There were local metastases to the orbit and paranasal sinus. Histopathology revealed infiltration of basaloid neoplastic epithelial cells into underlying dermis in cords and strands with peripheral palisading and stromal proliferation. Patient underwent exenteration of the affected eye along with radiotherapy. There has been no recurrence of tumour at 8 months post radiotherapy.*

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#### INTRODUCTION

Eyelid tumours are by far the most common neoplasms encountered in clinical ophthalmic practice [1]. Approximately, 90% of skin cancers arise in the head and neck region and 10% of them occur in the eyelid [2]. Basal cell carcinoma is the most common eyelid tumour and constitutes 80 - 90% of its bulk [3]. The second commonest eyelid tumour is the squamous cell carcinoma which forms 5-10% of the eyelid malignancy [4]. Basal cell carcinoma has little metastatic potential and squamous cell carcinoma has a reported metastatic rate up to 21% [5].

Basosquamous carcinoma (BSC) also known as metatypical carcinoma, basaloid squamous cell carcinoma or keratolytic basal cell carcinoma. They share the features of both squamous cell and basal cell carcinoma. Basosquamous carcinoma is an extremely rare epithelial malignancy of the eyelid with aggressive behaviour. They form less than 2% of incidence of all non-melanomas of the skin [6]. This malignant neoplasm is now considered a new variety of non-melanoma skin cancer with its own characteristics and histologic characteristics. In some cases, distinction between a basal cell and squamous cell carcinoma can be difficult and definitive identification of a BSC may be more challenging [7]. We are reporting a case report of a patient with presentation of BSC.

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#### CASE REPORT

A 53-year-old gentleman who was previously healthy, presented with enlarging mole of the left lower lid for the past 5 years. The lesion had grown progressively larger and became more violaceous with on and off contact bleeding in the past one year. Patient sought medical attention after 5 years of presentation when he developed left mechanical ptosis. The best corrected visual acuity (BCVA) was 6/7.5 in the right eye and hand movement in the left eye. Left ocular examination revealed an ulcerated and hyperpigmented mass over both upper and lower lid region with contact bleeding. The mass was hard and indurated associated with mechanical ptosis (Figure 1A). The bulbar and palpebral conjunctiva were congested with feeder vessels seen (Figure 1B). There was left eye relative afferent pupillary defect (RAPD). Anterior segment and fundus examination were normal. Examination of the right eye was unremarkable. There was no cervical lymphadenopathy.

A computed tomography (CT) scan of the orbit and brain revealed heterogeneously enhancing soft tissue mass in the lower, lateral, and posterior aspect of the left orbit. There was also involvement of left inferior rectus and left inferior oblique muscles with extension of mass to the anterior aspect of optic nerve. The mass extends superficially to lower



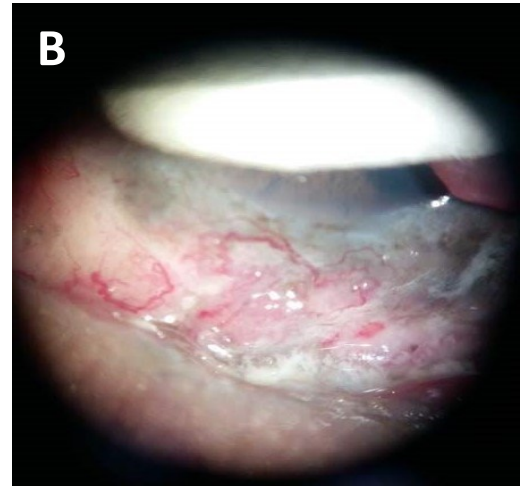


Figure 1A: Left mechanical ptosis with hyperpigmented and ulcerated lesion over the upper and lower lid.  
 Figure 1B: Left palpebral conjunctiva is congested with feeder vessels seen.



Figure 2A: Computed tomography (CT) scan of the orbit with axial view showing irregular heterogenous mass filling the intra and extraconal spaces within the left orbit (red arrow). Half of left lateral, medial and inferior recti muscles is involved with loss of the normal anatomical configuration and ocular space, causing deformed left globe.

Figure 2B: There is an extension of the mass to the anterior aspect of optic nerve. CT scan of orbit with coronal view showing mass extends superolaterally to left lacrimal gland, laterally to left zygoma and inferiorly into left maxillary sinus with associated bony destructions.

eye lid, superolaterally to left lacrimal gland, laterally to left zygoma and inferiorly into left maxillary sinus associated with bony destructions (Figure 2).

Subsequently, incisional biopsy was done. Histopathological examination showed infiltration of basaloid neoplastic epithelial cells into underlying dermis in cords and strands, forming reticulated pattern. The neoplastic cells showed peripheral palisading, and the surrounding stroma was desmoplastic with occasional mucin deposition seen. Tumour clefting from the stroma was observed as well. Immunohistochemical stains showed the neoplastic cells were diffusely positive for Epithelial antigen (Ber-EP4) and negative for Epithelial membrane antigen (EMA). Thereby, a histopathological diagnosis of left basal cell carcinoma was made.

In view that patient had left basal cell carcinoma with extensive extension into orbital and paranasal sinuses, patient was counselled for left extended exenteration and the surgery was proceeded (Figure 3A). Histopathological examination of the exenterated eye and paranasal sinus showed that the tumour was composed of islands, solid nests, cohesive sheets, and clusters of closely packed basaloid cells with round to oval nuclei and minimal cytoplasm. Foci of squamous differentiation were found. The tumour cells were Ber-EP4 positive. Areas of tumour necrosis and perineural invasion were also seen. Histopathological diagnosis of left eyelid BSC with orbital soft tissue and bone invasion was made.

A CT scan of the thorax, abdomen and pelvis revealed no metastases. At one month post

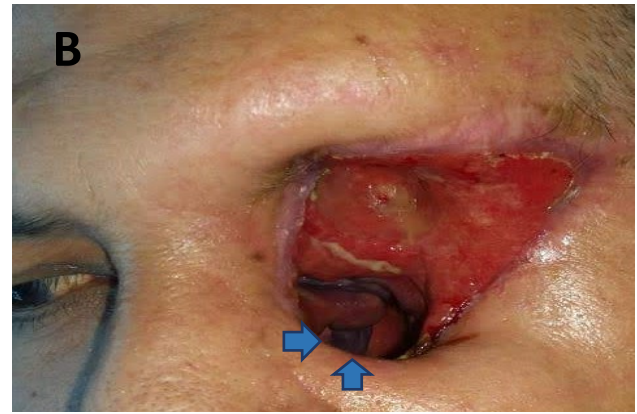


Figure 3A: Left eye mechanical ptosis with hyperpigmented and ulcerated mass causing destruction of eyelid architecture. Surgical excision area marked prior to exenteration.

Figure 3B: At one month post exenteration: the wound and socket is clean with healthy granulation tissue. Blue arrows indicate the maxillary sinus.

exenteration, the wound was clean and healthy granulation tissue observed (Figure 3B). Patient subsequently underwent radiotherapy. There was no recurrence noted at post radiotherapy.

## DISCUSSION

Basosquamous carcinoma was first described by Mac Cormac in 1910 as a rare tumour that formed less than 2% of the incidence of non-melanoma skin cancers. This histologic variant was reported in a series of rodent ulcer in which both basal cell and squamous cell carcinoma was present without any transition zone [8]. In 1974, the World Health Organisation confirmed BSC as a separate entity [9]. Previous studies have not provided the exact definition of BSC except for Burston and Clay. According to Burston and Clay, BSC is defined as BCC differentiating into squamous cell carcinoma [10].

Basosquamous carcinoma is a slow growing neoplasm but highly aggressive. There is a wide variation of clinical presentation of BSC as in our case report, which makes it difficult to differentiate BSC from squamous cell carcinoma.

Clinically BSC is indistinguishable from the basal cell carcinoma. Histologically, BSC is defined as a neoplasm with the features of basal cell carcinoma with foci of squamous differentiation and spindle cell areas. The tumour lobules are more irregular and peripheral palisading is less pronounced but focally present. Stromal proliferation is more prominent, as presented in our case [11].

Immunohistochemistry also aids in the diagnosis of BSC. Basal cell and squamous cell carcinoma can be readily distinguished using routine immunohistochemistry for Ber-EP4 and EMA [12]. Basosquamous carcinoma BSC showed an immunostaining pattern similar to that of basal cell carcinomas with Ber-EP4 positivity and with

negative staining for EMA, similar to our patient. Using the help of the immunohistochemistry, it could help in diagnostic certainty of this rare challenging BSC.

The treatment modalities for BSC are surgical excision, radiotherapy, and Mohs microscopic surgery [13]. Surgical excision is the treatment of choice. For BSC, surgical margins should be wider than those for low-risk basal cell carcinoma due to the infiltrative growth pattern of this tumour. However, despite a wide local excision, there has been high rate of recurrences reported. According to Borel et al, he reported a local disease recurrence rate of 45.7% after wide excision for BSC in 35 patients with a follow-up period of 1 year [14]. Another study done by Schuller et al, reported that a recurrence rate of 12.1% in 33 patients with BSC treated with surgical excision [15].

Adverse prognostic signs include perineural and lymphatic spread, similarly observed in our case. According to Petri et al, patients with perineural invasion have significantly higher rates of metastatic disease and local recurrence compared to patients without perineural invasion [16]. Thereby, a close and a long clinical follow up is needed for this aggressive primary tumour.

## CONCLUSION

In conclusion, BSC is a rare and aggressive form of carcinoma with propensity of lymph node and perineural spread. Most BSC arise in the head and neck, so in our case report, it provides important insights into this tumour entity. The rarity of this tumour, the pattern of growth, and the initial lack of diagnostic criteria have resulted in only a few studies evaluating the best treatment options for patients. Thereby, this tumour is rightly described as devil in disguise due to its aggressiveness and destructive behaviour.



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## Case Report

### SURGICALLY INDUCED SCLERITIS: A CASE SERIES

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#### ABSTRACT

*Surgical induced scleritis (SIS) is a potentially devastating complication following ocular surgeries. The objective of this case study was to review the clinical experience of SIS at Hospital Selayang. A retrospective observational case series review of SIS cases at Hospital Selayang from year 2008 to 2017. The result found that there were 13 patients with age ranging from 38 to 78 years old. Four patients (30.8%) had glaucoma filtering surgery, three (23.1%) had pterygium excision, three (23.1%) had scleral buckling and cryotherapy, two (15.4%) had cataract extraction and one (7.7%) had vitrectomy as the initial ocular surgery prior to onset of SIS. Majority (53.8%) had history of multiple ocular procedures. Necrotising scleritis was the commonest subtype. Eight patients (61.6%) achieved vision of  $\geq 6/24$ . Four patients (30.8%) had vision of  $\leq 6/60$ . In conclusion, SIS may have favourable visual prognosis when treated accordingly. Intraoperative cytotoxic agent usage in ocular surgeries should be with extreme care due to risk of SIS.*

#### INTRODUCTION

Despite its rarity, surgical induced scleritis (SIS) is distressing and has been observed following a variety of ocular procedures such as glaucoma filtering surgery, cataract extraction, pterygium excision, retinal detachment surgery, penetrating keratoplasty and strabismus surgery [1-9]. While immune mediated scleritis is quite commonly reported in patients with coexisting systemic illness like rheumatoid arthritis and other vascular collagen disorders and may occur in this group of patients after surgery, we report SIS in patients without any known underlying systemic vascular collagen diseases. This condition requires early recognition and prompt effective treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and immunosuppressive agents to prevent dreadful sequelae of loss of vision. Surgical induced necrotizing scleritis (SINS) is a severe form of SIS. Various etiological mechanisms, disease patterns, treatment administered, and visual outcomes is presented in this case series review.

#### METHODOLOGY

This is a retrospective case series over a 9-year period between 1<sup>st</sup> January 2008 and 31<sup>st</sup> December 2017. Electronic medical records of all patients who were diagnosed and treated as SIS in Ophthalmology clinic, Selayang Hospital between the period stated were retrospectively reviewed, which included a total

of 16 eyes from 16 patients. Thirteen eyes met the study criteria and thus included in this study. Scleritis was diagnosed clinically on the basis of a painful red eye with associated photophobia and blurring of vision. Surgical induced diffuse scleritis type was recognized by the presence of inflamed scleral tissue with congested deep episcleral vascular plexus usually adjacent to operative wound [4,10]. Surgical induced necrotizing scleritis type was identified by the presence of a localized patch of scleritis associated with acute congestion, avascular overlying episcleral tissue or scleral necrosis in advanced disease [10]. Finally, posterior scleritis type demonstrated presence of mainly posterior segment involvement such as choroidal detachment or effusion, exudative retinal detachment or disc edema; with the absence of marked anterior scleral involvement [11]. Depending on the severity of each condition, all of the above conditions portrayed clinical improvement either with non-steroidal anti-inflammatory drugs (NSAIDs), topical or oral corticosteroids with or without second-line immunosuppressive therapy. Demographic data, number and type of ocular surgeries performed, onset and clinical manifestation of disease, treatment modalities and visual acuity were collected and documented. Patients with evidence of infectious post-operative scleritis, known or newly diagnosed collagen vascular disease or autoimmune diseases or incomplete documentation were excluded from this case review.

## RESULTS

There were 13 patients involving 13 eyes in this study, with age at diagnosis ranging between 34 to 78 years old. There were nine males (mean age 56 years) and four females (mean age 78.5 years) affected. All patients had unilateral eye involvement. None of them had history of scleritis prior to surgery (Table 1).

In this case series, the mean interval between initial surgery to onset of SIS was 75.5 months (ranged five - 144 months). Four patients (30.8%) had glaucoma filtering surgery, three (23.1%) had pterygium excision, three (23.1%) had scleral buckling and cryotherapy, two (15.4%) had cataract extraction and one (7.7%) had vitrectomy as the initial ocular surgery done before occurrence of SIS (Table 2). Of the 13 eyes, seven (53.8%) had history of multiple ocular procedures (Table 3).

Most patients showed necrotising scleritis pattern which was identified in seven eyes (53.8%). The rest of the patients demonstrated either diffuse anterior scleritis (23.1%) or posterior scleritis (23.1%) (Table 4). Except from three patients (all males; two had necrotising scleritis; one had diffuse anterior scleritis), all other patients were screened and negative for autoimmune or connective tissue diseases.

We observed a variety of ocular surgical procedures which preceded the onset of necrotising scleritis in our patients (Table 4). Patients presented with a range of symptoms included eye redness, pain and some had reduced vision. In all patients, the site of scleral necrosis was intimately related to the previous surgical incision site. All patients were treated with immunosuppressive therapy (topical and oral prednisolone), however four out of seven (57.%) required second line

Table 1: Demographic data of patients.

Demography	Number of patients (n=13)
Gender	
Male	9
Female	4
Eye involvement	
Unilateral	13
Bilateral	0
Age (years)	
Range	Male (34-78) Female (44- 69)
Mean	Male (56) Female (78.5)

Table 2: Onset and cases of SIS by types of ocular surgery.

Types of Ocular Surgery	Number of eyes n=13 (%)	Onset of SIS* months (mean)
Glaucoma Filtering Surgery	4 (30.8)	5-26 (15.5)
- Trabeculectomy with MMC**	3 (23.1)	6-26 (16)
- Glaucoma Drainage Device	1 (7.7)	5
Cataract Extraction	2 (15.4)	49-84 (66.5)
- Phaco converted ECCE/ACIOL ***	1 (7.7)	49
- ICCE/Scleral Fixated IOL ****	1 (7.7)	84
Pterygium excision	3 (23.1)	60-144 (102)
- with MMC**	2 (15.4)	108-144 (126)
- unknown usage of MMC**	1 (7.7)	60
Scleral buckle/ Cryotherapy	3 (23.1)	5-24 (14.5)
Pars plana vitrectomy	1 (7.7)	19

\* surgical induced scleritis

\*\* mitomycin-C

\*\*\* anterior chamber intraocular lens

\*\*\*\* intraocular lens

Table 3: Number of ocular procedures prior to SIS

Single Procedure (n=6)
3 – pterygium excision
1 – trabeculectomy
1 – scleral buckle/ cryotherapy
1 - cataract extraction
Multiple Procedures (n=7)
2 - multiple glaucoma filtering surgeries
1 – cataract extraction followed by trabeculectomy
1 – cataract extraction followed by scleral buckle/ cryotherapy
1 – multiple retinal detachment repair surgeries
1 – vitrectomy followed by cataract extraction
1 – complicated cataract extraction (phaco converted ECCE <sup>*</sup> / anterior vitrectomy/ ACIOL <sup>**</sup> )

\* phacoemulsification converted extracapsular cataract extraction

\*\* anterior chamber intraocular lens

Table 4: Clinical manifestations of SIS.

	Diffuse	Necrotising	Posterior
Number of eyes, n (%)	3 (23.1)	7 (53.8)	3 (23.1)
Prior ocular surgery, (n)	(1) Cataract extraction (1) Trabeculectomy/ MMC (1) Vitrectomy	(2) Pterygium/MMC (1) Pterygium/unknown MMC (1) Scleral buckle/ cryotherapy (1) Cataract extraction (1) Scleral buckle/ cryotherapy followed by vitrectomy (1) Cataract extraction followed by scleral buckle/ cryotherapy	(2) Multiple glaucoma filtering surgeries/ MMC (1) Cataract extraction followed by trabeculectomy/ MMC
Second line therapy, n (%)	0 (0)	4 (57.1)	2 (66.7)
Visual outcome, n (overall %)			
≥6/24	2 (15.4)	5 (38.5)	1 (7.7)
6/36- 6/60	-	-	1 (7.7)
<6/60	1 (7.7)	2 (15.4)	1 (7.7)

immunosuppression (Methotrexate or Azathioprine) to control disease activity. With appropriate treatment, most (71.4%) had good visual outcome of 6/24 or better. One patient had vision of counting finger at 2 feet due to progression of underlying glaucoma. Another patient who underwent pterygium excision with mitomycin C (MMC) experienced a more severe form of scleritis whereby he had scleral necrosis with microperforation requiring lamellar grafting alongside second line immunosuppressive therapy. He had two episodes of disease reactivations while on tapering dose of oral prednisolone 7.5mg daily. Disease control was achieved after 15 months of initial diagnosis with Methotrexate 10mg weekly while maintaining long-term low dose of oral prednisolone 5mg daily.

Despite treatment, he had poor final visual outcome of counting finger at 2 feet attributed by dense cataract and maculopathy secondary to age-related macular disease. Full autoimmune and connective tissue workup which consisted of erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), viral and syphilis serology, Mantoux and chest X ray test results were not significant for this patient. Figure 1 shows anterior segment photos of patients with necrotising scleritis.

Posterior scleritis was observed in three patients. Apart from typical symptoms of eye pain and redness, patients significantly complained of deterioration of vision. All three patients demonstrated signs of posterior scleral

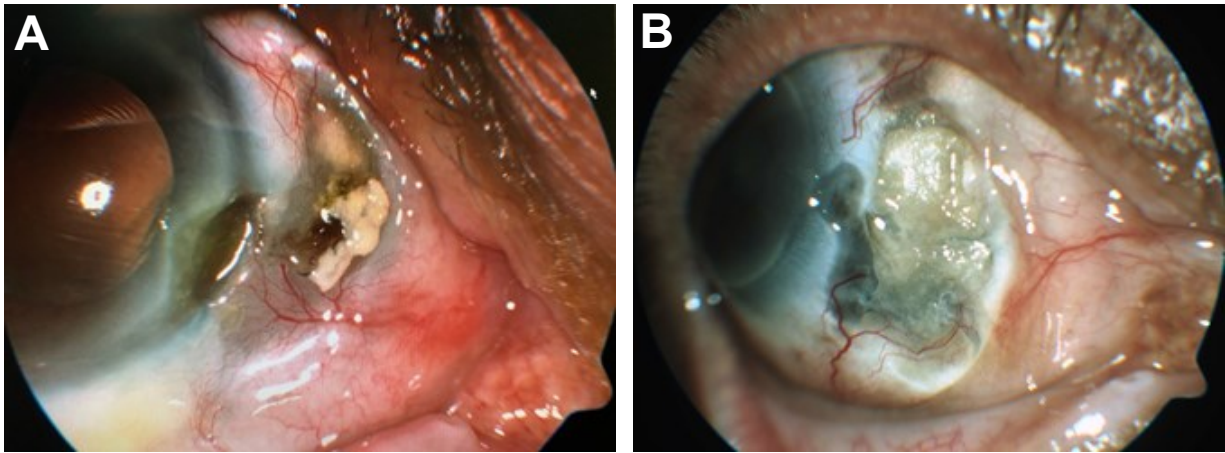


Figure 1: (A, B) Anterior segment photo of two patients with focal area of scleral necrosis with adjacent inflammation following pterygium excision with mitomycin C usage.

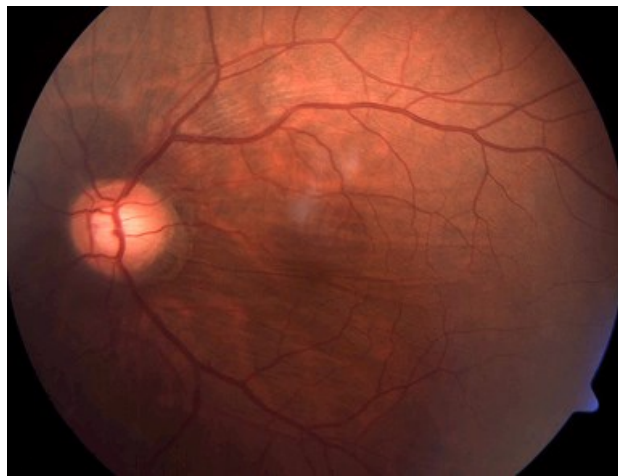


Figure 2: Chorioretinal folds in a patient with posterior scleritis.

inflammation such as choroidal detachment, thickening of sclera (all had more than 1.8mm scleral thickness), chorioretinal folds and presence of fluid in subtenon space (T- sign) which were evident on B scan ultrasonography. Patients showed more aggressive disease spectrums whereby two patients experienced multiple episodes of disease reactivations upon oral prednisolone tapering, despite early addition of second-line immunosuppression. One patient had light perception only vision during her last review. She had two trabeculectomy with MMC and one glaucoma drainage device implantation surgery performed prior to the onset of posterior scleritis. She was treated with topical and oral prednisolone (at dose of 1mg/kg daily with subsequent tapering) for about two months duration during the first episode of scleritis. Azathioprine was added subsequently when her disease recurred after three months of immunosuppressive free period. Unfortunately, due to low absolute lymphocyte count ( $0.5 \times 10^9/L$ ) Azathioprine was later withheld. During one of three episodes of disease reactivations, intravenous methylprednisolone was required to control the disease. Nevertheless her disease progressed with development of appositional (kissing) choroidals. Her eye later became phthisical with visual acuity of only light perception. Figure 2 shows

a patient with posterior scleritis with chorioretinal folds.

Diffuse type of post-operative scleritis showed a more benign spectrum of disease. This was seen in three patients in which disease activities were adequately controlled using oral non-steroidal anti-inflammatory drugs (NSAIDs) and topical prednisolone only. All patients experienced ocular redness and pain and clinically diffuse scleral inflammation adjacent to site of previous surgical wound were observed. One patient had the characteristic severe pain which awakened him from sleep. Anterior chamber activity was documented in two of the patients. Nevertheless patients with diffuse anterior scleritis showed generally milder course of illness and had good visual outcome. Only one patient documented poor vision of hand movement due to pre-existing myopic maculopathy.

## DISCUSSION

Glaucoma filtering surgery has shown to be the leading cause of surgical induced scleritis (SIS) in our centre likewise previously reported [12]. Mean

time to presentation from surgery has been reported as 9 months ranging from day one to 40 years by others [6,12]. However, in our case series, the onset of disease ranged from 5 months to 12 years (144 months) post initial surgery, with glaucoma filtering surgery showing the earliest onset of scleritis. Interestingly in our case series, post-operative scleritis involved more male patients. E O'Donoghue at al documented predominance of females patients (70%) and linked it to the increased associations of autoimmune diseases in this group of patients [6]. Contrary, we excluded patients with autoimmune or collagen vascular diseases thus similar observations were not observed. Majority of patients (53.8%) had history of multiple ocular procedures which were consistent with reports from previous authors[6,14]. An increased number of ocular procedures have previously been associated with higher incidence of SIS, similarly seen in our study.

In our centre, most patients demonstrated necrotising scleritis pattern followed by diffuse anterior scleritis and posterior scleritis [6,15]. Necrotising scleritis is a rare but possible sequelae of ocular surgery. Despite its rarity, this subtype of scleritis is the commonest to be associated with following surgical procedures [6,14]. Surgical induced necrotising scleritis (SINS) represents a more severe form of disorder requiring early aggressive immunosuppression to control disease activity and reduce ocular complications [16]. Extensive sclera destructions and necrosis may warrant prolonged, potentially hazardous immunosuppressive therapy requirement in some patients [17]. More aggressive disease can present with scleral thinning and perforation necessitating lamellar graft which was done in 1 of our patients. Another patient recorded poor vision due to underlying glaucoma which made worst by the use of prolonged immunosuppressive medications. Our findings showed that good visual outcome was achievable by most patients with SINS hence proving that early diagnosis and prompt treatment results in good visual outcome [1]. On the other hand, diffuse anterior scleritis represents a more benign and self-limiting condition, where treatment with oral non-steroidal anti-inflammatory drugs (NSAIDs) adequately controlled disease activity [4,17]. These observations were seen in all of our patients diagnosed with diffuse anterior scleritis whereby they showed milder spectrum of disease which completely responded to oral NSAIDs. Posterior scleritis more often carried a poorer visual prognosis despite optimal management instituted [16,17]. Similarly to necrotising scleritis, patients often require systemic corticosteroid with or without second line immunosuppression in the form of immunomodulating agents (Azathioprine, Methotrexate, Mycophenolate Mofetil) to achieve disease control [18]. Posterior scleritis carries most threat to vision due to the involvement of the retina, choroid and optic disc [17]. In our patients, only one third of patients with posterior scleritis achieved vision of 6/24 or better. Recurrences in SIS are not uncommon and were seen in our patients particularly in the necrotising and posterior scleritis subtypes[14].

The precise underlying mechanism of SIS remains unknown to date. As proposed by Watson, local vascular closure in the sclera was contributed by both mechanical trauma (including surgery) and biological trauma such as infections and immune complexes [16]. The resultant hypoxic condition initiated a chain of catabolic events leading to progressive scleral necrosis. Clinicopathological study by Maite de Sanza et al have demonstrated evidence of immune complex mediated vasculitis following observation of increased deposition of inflammatory cells and HLA-DR expression in the scleral tissues of post-operative scleritis patients [19]. While scleritis has been linked with various connective tissue disorders, in majority of cases, evidence of underlying diseases could not be detected [10]. In a clinical-pathologic review of post-operative scleritis by Rishi et al, patients who developed SINS were those with underlying systemic autoimmune diseases [12]. They also postulated that pterygium surgery with or without use of adjunctive agents were associated with higher rate of secondary infection which contributed to scleral inflammation and necrosis. In our case series, pterygium excision surgery was the second commonest ocular procedure performed prior the onset of scleritis, and except one patient (who was not screened for systemic disease), rest of them did not have evidence of systemic vasculitic disease. Except in one case who complained of on and off eye discharge for one year (whereby the swab culture taken was negative), we did not find other evidence to suggest possible concurrent infection in the rest of the patients. Being a retrospective study, our findings and observations is also limited by the involvement of multiple ophthalmologists ,with various level of experience in the managements.

The risk of scleritis increases with the use of anti-metabolites, such as MMC in trabeculectomy and pterygium operation<sup>1</sup>. Mitomycin C is an antineoplastic antibiotic agent isolated from *Streptomyces caespitosus*. It alkylates and cross-links DNA thus inhibits protein synthesis and imposes long term inhibition to cellular proliferation [20]. Ischemic scleral necrosis induced by excessive cauterization during bare sclera technique is another possible cause of scleral necrosis [21]. Cheng HC et al has suggested intra-operative usage of lower concentration of MMC ie 0.02% for a safer yet effective technique to reduce the recurrence rate after bare sclera excision of pterygium [22]. Use of MMC in high risk patients with eye conditions which predisposed to poor wound healing such as Sjogren syndrome, keratoconjunctivitis sicca, meibomitis or blepharitis were not advisable as they were more likely to develop complications. Alternatively, pterygium excision with conjunctival autografting may provide better option in effort to reduce intraoperative MMC usage [12].

## CONCLUSION

SIS when treated according and promptly has a favorable visual prognosis. In this case series,

glaucoma surgeries with intraoperative cytotoxic agent usage is leading cause of surgical induced scleritis. Hence usage of this cytotoxic agent should be with extreme care.

#### DECLARATION OF CONFLICT OF INTEREST

The authors report no conflict of interest.

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## Case Report

### CEREBRAL VENOUS SINUS THROMBOSIS SECONDARY TO ISOLATED MAXILLARY SINUSITIS AND MSSA BACTEREMIA: A CASE REPORT

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#### ABSTRACT

*Cerebral venous sinus thrombosis (CVST) is a rare life-threatening condition related to high mortality and morbidity. The diagnostic challenge arises as patient may be asymptomatic or present with a variety of constitutional and neurological symptoms. We report a case of CVST in a young immunocompetent male. A 19 years old boy with no other comorbidity presented with sudden onset of fever, right jaw and temple pain, was referred to Ophthalmology team for right ptosis. Upon examination and prompt diagnosis, extensive dural venous sinus thrombosis with right cerebral convexity subdural effusion, right submandibular, parapharyngeal and retropharyngeal collections were detected through radiological imaging. Right maxillary sinusitis as the source of infection was also detected. The patient underwent maxillary sinus drainage and successfully treated with systemic antibiotics and anticoagulants. We highlight the importance of early suspicion of systemic involvement in patients presenting with eye symptoms. Prompt diagnosis, emergent radiographic evaluation, multidisciplinary approach and appropriate treatment with anticoagulants and antibiotics can improve survival and visual prognosis.*

#### INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a rare life-threatening condition [1] related to high mortality and morbidity. It poses a diagnostic challenge as patient may be asymptomatic or may present with a variety of constitutional and neurological symptoms ranging from fever, headache, altered consciousness, cranial neuropathies or stroke, and often requiring radiological guidance [2,3]. Cerebral venous sinus thrombosis can be categorized etiologically into primary/idiopathic or secondary causes, further divided into infective or non-infective. Non-infective causes may be due to coagulation disorders, neoplasms, homocystinuria, vasculitis or head trauma [4]. Infective causes are more common, with the most common being acute sinusitis specifically the sphenoid and ethmoid sinusitis, commonly attributed to *Staphylococcus Aureus* infection [3,5]. Failure to diagnose and treat the primary infection may result in devastating outcome. Favourable outcome depends on recognition, prompt broad spectrum antibiotic treatment and surgical control of the primary focus [6].

We report a case of CVST in a young immunocompetent male with acute maxillary sinusitis, an uncommon site of spread of infection complicated with Methicillin sensitive *Staphylococcus aureus* (MSSA) bacteremia. Prompt investigations and diagnosis were made with multidisciplinary approach and with initiation of

antibiotics and anticoagulants, severe life-threatening complications were prevented.

#### CASE REPORT

A 19-year-old young male with no past medical history was referred by Emergency Department to Ophthalmology team for mild right ptosis. He presented with high grade fever and excruciating right jaw pain extending to the right preauricular region and right temple. There were no other symptoms of increased intracranial pressure such as nausea or vomiting.

On examination, he was alert, conscious but febrile with a temperature of 38.5 degree Celsius. He had mild right conjunctival injection with mild ptosis and mild swelling over the right temple. All other vital parameters were unremarkable. Best corrected visual acuity (BCVA) was 6/12 and 6/9 in the right and left eye respectively. Neuro-ophthalmologic assessment showed no anisocoria, no relative afferent pupillary defect (RAPD), no visual field defect by confrontation test and colour vision was normal. The intraocular pressures were normal. There was no proptosis, or periorbital swelling. The anterior segments examination was unremarkable in both eyes. On fundoscopy, there was no evidence of optic disc swelling. He had limited



supraduction of the right eye with no limitation of other gazes and no diplopia were elicited (Figure 1).

He had right jaw tenderness extending to the right temple associated with inability to open his mouth. Dental and otorhinolaryngology examination was unremarkable.

Infective and thrombophilia screening was done. Total white cell count was  $13.47 \times 10^9/L$  with neutrophil predominance, Erythrocyte Sedimentation Rate (ESR) of 71 mm/hour and C-Reactive Protein of 349 mg/dl. Viral and diabetic screening was negative. There was no hypercoagulable state, values of complement 3 and 4 were normal. International Normalized Ratio (INR) was 1.67, fibrinogen 445, and prothrombin time 19.4.

Contrast Enhanced Computed Tomography (CECT) of orbit and neck showed thrombosis in the superior sagittal sinus, cavernous sinus, right sigmoid sinus extending to the right proximal internal jugular vein (IJV) with no venous infarct or acute intracranial bleed. There was right cerebral convexity subdural effusion with mild cerebral oedema. There was also submandibular, parapharyngeal, retropharyngeal, carotid space and small temporalis muscle collections over the right side. Right masseter, temporalis and pterygoid muscles were bulky. Right Fossa of Rossenmuller (FOR) was obliterated with fullness of nasopharynx as well as oropharynx. Evidence of right maxillary sinusitis were also seen (Figure 2).

While awaiting for his blood culture and sensitivity (C&S), he was treated empirically with high dose of intravenous (IV) Ceftriaxone and anticoagulant Enoxaparin. He was also started on anti- epileptics IV phenytoin 100 mg thrice a day as prophylaxis against possible seizure.

On Day 3 of presentation, worsening of supraduction and abduction of right eye was seen associated with

chemosis and injection in keeping with orbital cellulitis. The right intraocular pressure increased to 26 mmHg, with otherwise normal neuro-ophthalmologic assessment. There was no optic disc swelling. He was given additional topical moxifloxacin and timolol maleate.

Blood C&S grew Methicillin Sensitive *Staphylococcus aureus* (MSSA). Diagnosis of cerebral venous sinus thrombosis (CVST) secondary to maxillary sinusitis with MSSA bacteremia was made. Ophthalmologically patient had right orbital cellulitis with superior division third nerve palsy secondary to CVST.

He was then covered with IV Ceftriaxone and Cloxacillin for 6 weeks and was started on oral warfarin 3 mg 8 hourly, with dosage adjustments made based on daily INR. Otorhinolaryngology team performed the drainage of maxillary sinus.

After two weeks of medication, patient was afebrile and appeared more comfortable. Repeat Blood C&S showed no growth. Eye examination however showed persistence of mild right ptosis without any limitation in extraocular muscle movement. Chemosis and injection of right eye resolved with normal intraocular pressure. Fundoscopy however showed blurred disc margin of both optic disc. Enlarged blind spot on Bjerrum proves presence of papilloedema which was absent prior.

A repeat CECT brain and neck (Figure 3) showed worsening of right cerebral convexity subdural collections with suspicious intraparenchymal extension, dural and leptomeningeal involvement and cerebral oedema. However, there was resolving right submandibular, resolved superior sagittal sinus CVST with residual filling defects in right cavernous sinus, right sigmoid sinus extending to right IJV.

Due to worsening of cerebral collections and oedema, Infectious Diseases team started the



Figure 1: Shows 9 cardinal direction of gaze, right ptosis, mild injection of right conjunctiva and limitation of right supraduction.

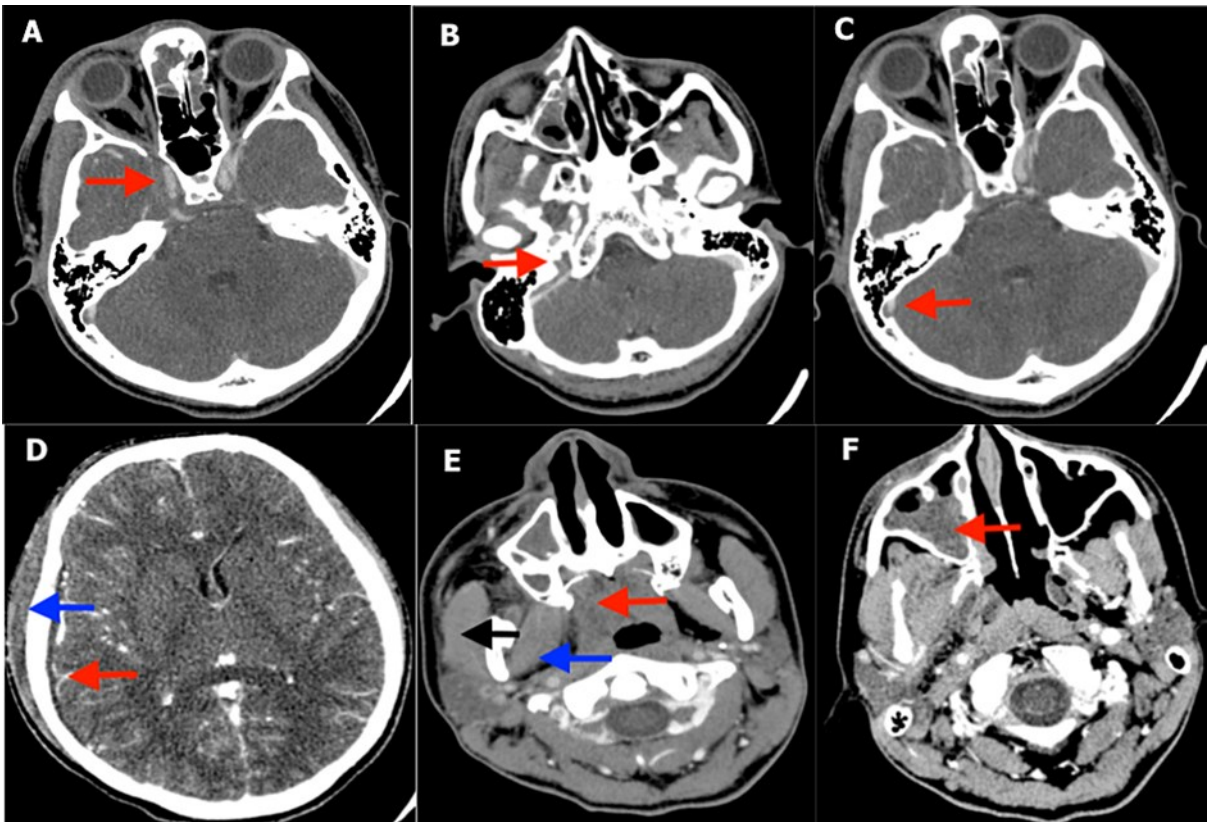


Figure 2: Axial brain Contrast Enhanced Computed Tomography:

- A. Shows filling defect within right cavernous sinus
- B. Filling defect within right jugular bulb
- C. Filling defect within right sigmoid sinus
- D. Right cerebral convexity with iso to hypodense subdural collection (red arrow) and swollen right temporalis muscle (blue arrow)
- E. Right fullness of nasopharynx and oropharynx (red arrow), right bulky pterygoid muscle (blue arrow) and masseter muscle (black arrow)
- F. Near total opacification of the right maxillary sinus, consistence with right maxillary sinusitis.

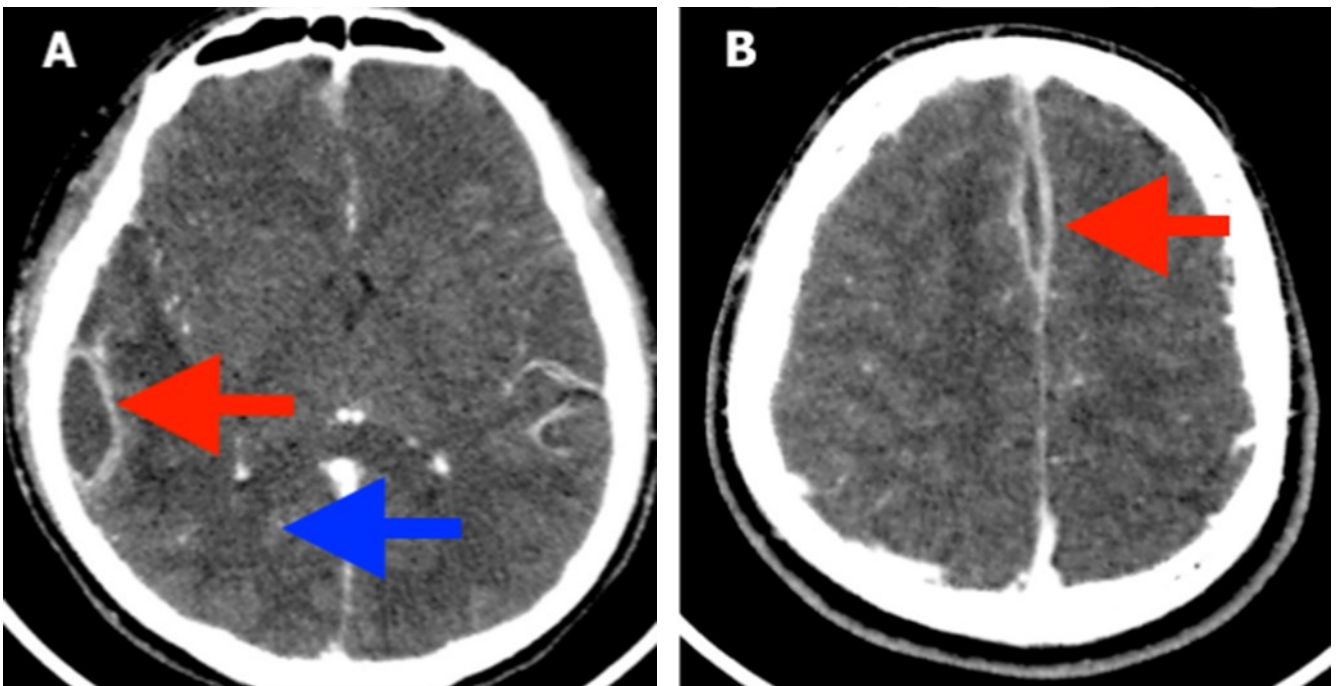


Figure 3: Axial brain CECT : **A.** Shows worsening right cerebral convexity hypodense subdural collection with suspicious intraparenchymal extension, dural and leptomenigeal involvement (red arrow) as well as cerebral oedema (blue arrow). **B.** Shows hypodense collection in the interhemispheric fissure.



patient on IV Meropenem which has better coverage in MSSA related complications and continued the IV Cloxacillin. Biopsy of right level 5 lymph done revealed chronic inflammation histologically. *Mycobacterium Tuberculosis* bacteria was not detected and neither was there evidence of tuberculosis infection radiologically or pathologically.

At completion of 6-weeks course of antibiotics, patient showed complete resolution of the ocular changes with no ptosis, no limitation of eye movements (Figure 4) and no papilloedema. He was afebrile and well.

## DISCUSSION

In cerebral venous sinus thrombosis, prothrombotic condition is almost always present. In the absence of prothrombotic condition, as seen in our patient, it is nearly always related to infective causes [6]. The spread of infection is commonly from the paranasal sinuses, mid face and orbit [7]. The case we reported here had the spread of infection from the maxillary sinus which is rarely involved in CVST [4].

Our patient developed Methicillin sensitive *Staphylococcus aureus* septicaemia from

maxillary sinusitis and progressed to extensive cerebral venous sinus thrombosis involving all major cerebral venous sinuses with collections extending into the pharyngeal spaces. One would expect a patient with an extensive involvement of CVST to present with increased intracranial pressure symptoms, pupillary dilatation and complete ophthalmoplegia with sinusitis symptoms like rhinorrhea, facial pain and tenderness of maxillary sinus. Our patient however did not present with such alarming signs.

All cerebral venous sinuses are valveless, thus they facilitate forward or backflow of blood allowing pathogens and neoplastic cells to travel to different parts of the brain. Infection coming from layers of the face can easily travel into the cavernous sinuses leading to the development of a thrombus resulting in cavernous sinus thrombosis. This condition may result in the swelling of the affected sinuses and damage to the surrounding cranial nerves [8]. Common symptoms include ptosis, proptosis, chemosis, ophthalmoplegia (cranial nerve [CN] III, IV, VI), and loss of sensation in the ophthalmic and maxillary divisions of the trigeminal nerve (V1 and V2) [7].



Figure 4: Shows resolution of ptosis and conjunctival injection as well as improvement of extraocular movements. Repeated CECT brain and neck (Figure 5) showed resolved CVST. Patient was discharged with oral warfarin 3.5mg OD and INR of 2.20. He ultimately made a full recovery.

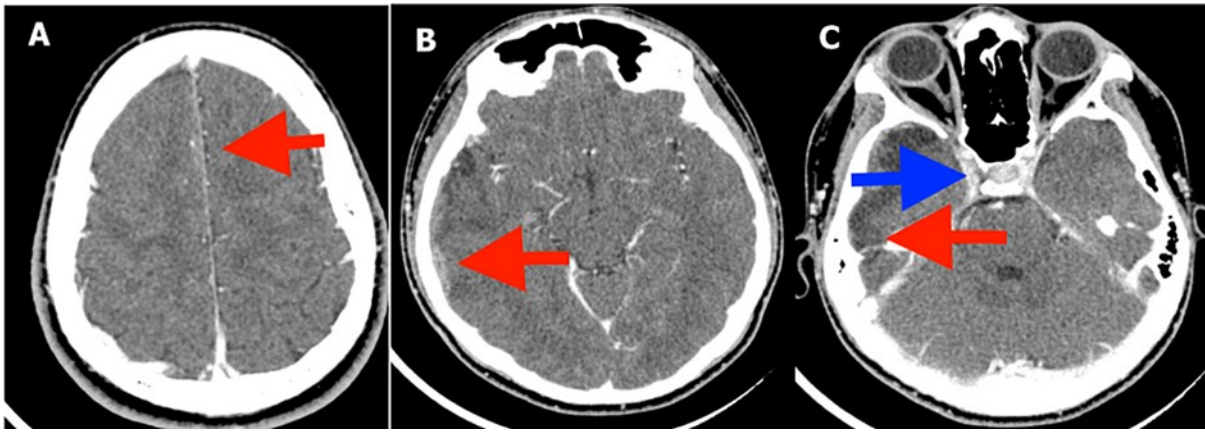


Figure 5: Axial brain CECT upon completion of treatment :**A.** Resolved interhemispheric collection **B.** Smaller residual of right cerebral convexity subdural collection  
**C.** Resolving right temporal parenchymal collection with residual dural enhancement (red arrow) and minimal residual filling defect in cavernous sinus (blue arrow).

The outcome of CVST varies from a complete recovery to death. Although most patients with CVST are discharged with favourable outcome, 18.9% of patients succumb to death or dependency according to the International study on cerebral vein and dural sinus thrombosis (ISCVT) [9]. Most patients treated promptly with anticoagulants had good prognosis [10].

Our patient who presented with unilateral ptosis, fever and jaw pain, an immediate multidisciplinary team management was carried out and an immediate radio imaging aided us to the diagnosis and etiology (maxillary sinusitis). Prompt biologic investigations and initiation of antibiotics and anticoagulants had also helped us in treating the underlying MSSA and the CVST. The Otorhinolaryngology team had eliminated the source of infection by surgical drainage. Series of clinical and radiological examination had helped us in managing this patient with an excellent outcome for such an extensive CVST.

## CONCLUSION

Early recognition and treatment of CVST has reduced mortality rate over time. Despite being a rare disease, CVST is frequently associated with catastrophic outcomes if it is not timely treated. Our case discussion highlights the importance of early suspicion of systemic involvement in patients presenting with ocular symptoms. Prompt diagnosis, emergent radiographic evaluation, multidisciplinary approach and appropriate treatment with anticoagulants and antibiotics can improve survival and visual prognosis.

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## Case Report

### VOGT KOYANAGI HARADA DISEASE: A CASE OF FAST RECURRENT

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anemia

#### ABSTRACT

A case report of a young lady diagnosed with Vogt-Koyanagi-Harada (VKH) disease with fast recurrence. An 18-years-old Maldivian lady presented with bilateral painless blurring of vision in both eyes (OU) for 1 week associated with redness. She also complained of severe headache and upper back pain. Her visual acuity (VA) was counting finger in the right eye (OD) and 1/60 in the left (OS). Anterior chamber revealed granulomatous reactions. Funduscopy revealed bilateral swollen optic disc, multiple punctate choroiditis and inferior exudative retinal detachment. Kernig sign was positive on neurological assessment. Optical computer tomography (OCT) of the macula showed multiple serous subretinal detachment OU. Fundus fluorescein angiography (FFA) OU revealed delayed choroidal filling, OU discs leakage, and multiple punctate hyperfluorescence with leakages. Infective screening was negative. There was marked visual gain to 6/12 after 3 days of intravenous Methylprednisolone., she was subsequently started on tapering dose of oral Prednisolone. Initiation of second line immunosuppressant was delayed due to incidental findings of anemia on blood investigation. The disease relapsed while she was on high dose of Prednisolone. Visual acuity was significantly reduced and OCT showed reappearance of subretinal fluid which required a second cycle of intravenous Methylprednisolone. This case highlights the importance of aggressive therapy in the case of VKH disease. Early commencement of other immunosuppressive therapies and the use of biologics need to be considered as a first-line treatment in severe cases.

#### CASE REPORT

An 18-year-old Maldivian lady with no known medical illness, presented with one-week history of bilateral progressive, generalized, painless blurring of vision associated with redness as well as headache and upper back pain. There was no previous history of ocular trauma or surgery. Visual acuity was counting finger in the right eye (OD) and 1/60 in the left eye (OS). Pupillary reactions were sluggish bilaterally. Anterior segment examination revealed bilateral granulomatous panuveitis, anterior chamber cells of 2+, the presence of keratic precipitates and busacca nodules. Funduscopic findings include bilateral optic disc swelling, macula oedema, as well as multiple punctate choroiditis associated with inferior exudative retinal detachment (Figure 1a-b). Intraocular pressure was normal in both eyes. Neurological examination revealed a positive Kernig sign, however there was no other neurological signs found.

Optical computer tomography (OCT) of the macula showed multiple serous retinal detachment OU (figure 2a-b). Fundus fluorescein angiography (FFA) revealed delayed choroidal filling, discs leakage, and multiple punctate hyperfluorescence with leakages bilaterally (figure 3a-b). Blood investigation including erythrocyte sedimentation rate and infective screen-

ing were all normal except for a hypochromic microcytic anemia. Her Mantoux test was 0 mm. A diagnosis of bilateral acute Vogt-Koyanagi-Harada disease was made.

She was immediately started on intravenous methylprednisolone 250mg QID for three days, followed by oral prednisolone 60mg daily (1mg/kg/day). Topically she received Prednisolone acetate 1%, Mydracyl 1%. Best corrected visual acuity (BCVA) markedly improved to 6/12 OD and 6/18 OS upon completion of intravenous methylprednisolone. Initiation of second-line immunosuppressant was deferred due to the anemia which warranted further investigation. While on the high dose of the oral prednisolone, her vision deteriorated due to recurrent multifocal choroiditis and subretinal fluid which was seen on OCT. She was then readmitted for another cycle of intravenous methylprednisolone. Unfortunately, the patient was loss to follow-up thereafter.

#### DISCUSSION

Vogt-Koyanagi-Harada (VKH) disease is a multisystem granulomatous inflammatory autoimmune disorder with ophthalmic, dermatologic, neurologic and auditory manifestations. The ocular





Figure 1: Fundus photography OD (1a) and OS(1b) show optic disc swelling with multiple punctate choroiditis.

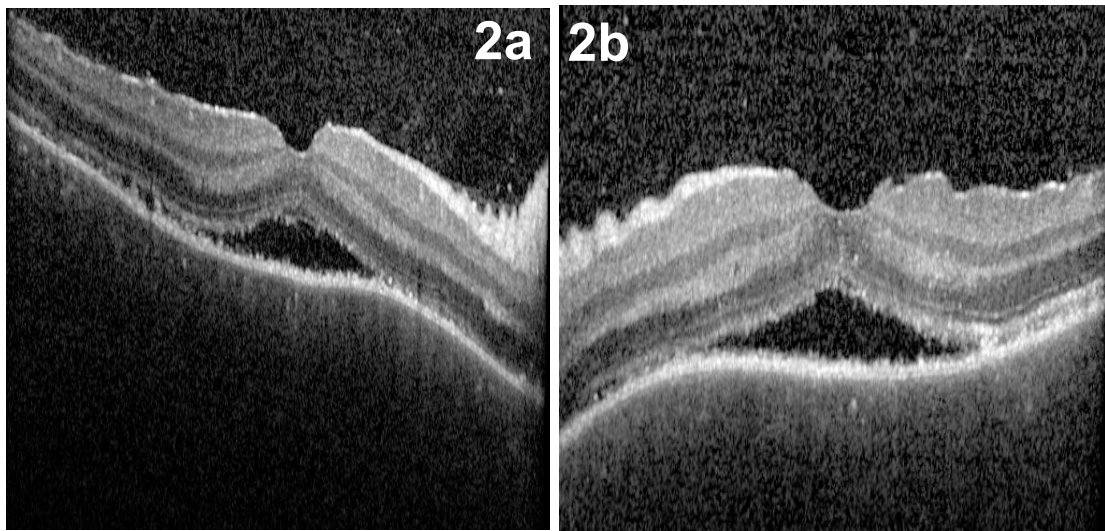


Figure 2: OCT of macula: OD (2a) and OS (2b) show the presence of subretinal fluid.

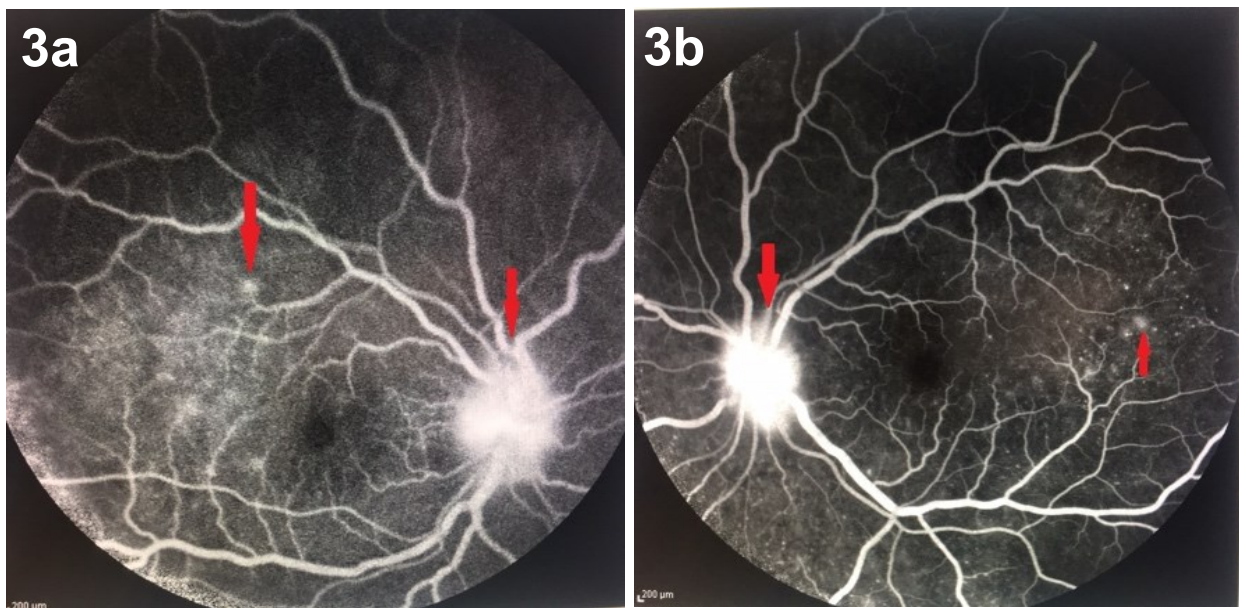


Figure 3: Fundus Fluorescein Angiography: OD (3a) and OS (3b) show disc leakages and multiple hyperfluorescence with leakages.

manifestations include severe panuveitis with iridocyclitis, diffuse choroidal swelling, serous retinal detachment and optic disc hyperaemia. Patients can present with bilateral granulomatous panuveitis with or without extraocular manifestations [1]. Incidence of VKH disease varies depending on the geographic location and ethnicity. Darkly pigmented races are primarily affected such as Hispanics, Asians, and Asian Indians. It mostly affected female and patients in their fifth decades of life [2].

The diagnostic criteria of VKH disease based on the recommendation by The American Uveitis Society in 1978 includes (1) the absence of any history of ocular trauma or surgery; and (2) the presence of at least three of the following four signs: (a) bilateral chronic iridocyclitis; (b) posterior uveitis, including exudative retinal detachment, forme fruste of exudative retinal detachment, disc hyperaemia or oedema and "sunset-glow" fundus; (c) neurologic signs of tinnitus, neck stiffness, cranial nerve, or central nervous system disorders, or cerebrospinal fluid pleocytosis; and (d) cutaneous findings of alopecia, poliosis, or vitiligo. However, other disease entities such as sympathetic ophthalmia, ocular syphilis, posterior scleritis and acute posterior multifocal placoid pigment epitheliopathy may have similar presentation with VKH disease and needed to be ruled out first [1].

The aim of treatment in the acute stage is to halt the disease process from entering the chronic recurrent phase. Standard treatment includes oral prednisolone (1 – 1.5 mg/kg) or initial intravenous methylprednisolone, preferably within 2 weeks from the beginning of symptoms, followed by slow tapering of oral corticosteroids. Treatment should be no less than 6 months and the dose should be titrated according to the severity of the inflammation [2].

Immunomodulators such as azathioprine and methotrexate in combination with corticosteroids as first-line therapy have been reported to significantly reduce the recurrence rates, late complications and improvement in visual outcome in acute disease [2]. In our case, the initiation of the immunomodulator was delayed due to the fear of bone marrow suppression effects causing deterioration of anemia which was incidentally found during investigation. Hematological toxicity is a serious and potentially life threatening effect which presents as myelosuppression and pancytopenia, which can occur even on low dose immunomodulatory treatment [3].

Biologics are recently studied medication and have been used widely for the treatment of non-infectious uveitis and other ocular inflammatory diseases. It has been used as an alternative or as an adjunct treatment in patients with inadequate response or intolerance towards conventional immunotherapy. Biologics agents such as Infliximab and Adalimumab (anti – TNF) have been reported to be an effective treatment of VKH disease [2]. It was reported to significantly increase the hemoglobin value based on studies in a patient with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis [2,4,5].

This case highlights the importance of aggressive therapy in Vogt-Koyanagi-Harada disease. In cases where immunomodulators cannot be commenced, early consideration of biologics such as infliximab and adalimumab should be sought to prevent the progression of this potentially blinding condition.

#### **DECLARATION OF CONFLICT OF INTEREST**

The authors report no conflicts of interest.

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## Case Report

### INFLAMMATORY LENS DEPOSITION FOLLOWING SUPRAMID RIPCORD REMOVAL

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#### ABSTRACT

*This is a case report of anterior chamber inflammation after removal of Supramid<sup>®</sup> intraluminal Stent suture used to prevent postoperative of hypotony in a patient with non-valved Glaucoma drainage device (GDD). Removal of Ripcord Supramid<sup>®</sup> intraluminal stent from glaucoma drainage device caused sudden ocular decompression and hypotony; this induced breakdown in the blood-aqueous barrier (BAB) causing anterior uveitis and deposition on the anterior surface of the intraocular lens. In conclusion, hypotony following removal of the intraluminal Supramid<sup>®</sup> stent result in intraocular inflammation.*

#### INTRODUCTION

Intraocular damage caused by uveitis can result in increased intraocular pressure (IOP), with subsequent damage to the optic nerve [1]. Several factors may be involved in the pathogenesis of inflammatory glaucoma, including obstruction of the trabecular meshwork by inflammatory cells and proteins, trabeculitis (inflammation of the trabecular meshwork), formation of peripheral anterior synechiae, posterior synechia leading to pupillary block, iris neovascularization and neovascular glaucoma, and anterior rotation of the lens-iris diaphragm [2]. Additionally, the use of steroids to control the inflammatory process may cause secondary elevation of IOP. Inflammation associated IOP elevation and glaucoma may become a severe complication and contribute to visual loss in patients with uveitis [3].

Glaucoma is defined as the presence of either pathologic cupping of the optic disc and/or a glaucomatous visual field defect with elevated IOP above 21 mm Hg [4]. The only known modifiable factor is intraocular pressure (IOP). Therefore treatment is focused on lowering IOP through medical or surgical therapy. Surgical therapy is indicated when medical or laser therapies fail to provide adequate IOP control to slow down the progressive optic nerve damage [5].

Tube shunt surgery has a higher success rate compared to trabeculectomy during the follow-up period [5]. It is also indicated in patients with refractory glaucoma which have a high risk of trabeculectomy failure [5]. Glaucoma drainage devices (GDDs) are composed of a silicone tube (~0.3 mm inner diameter) connected to a plate that drains aqueous humor from the anterior chamber to the subconjunctival space. Glaucoma drainage devices can be valved to restrict flow below a certain level of IOP, such as the Ahmed glaucoma valve (New World Medical, Rancho Cucamonga, CA), or non-valved such as the 350 mm<sup>2</sup> Baerveldt glaucoma implant (BGI Abbott Medical Optics, Santa Ana, CA).

Studies have shown that the BGI has comparable outcomes to glaucoma filtration surgery [6]. The BGI requires the use of a stent suture inserted within or around the tube lumen to restrict the aqueous flow initially following device insertion in order to prevent the initial hypotony. The stent is often removed several months later [6]. We report a case of intraocular inflammation after supramid ripcord removal causing inflammatory lens deposition in a young man with advanced steroid-induced glaucoma requiring BGI implantation.



## CASE REPORT

A 44-year-old Malay gentleman, with a history of bilateral idiopathic anterior uveitis was referred to our glaucoma clinic for further management. The patient has glaucoma secondary to anterior uveitis, and is also known to be a steroid responder causing bilateral advanced glaucoma. He has been on treatment for glaucoma in the last 20 years.

He underwent trabeculectomy surgery on the right eye twice and left eye once. Intraocular pressure in the left eye was controlled after the trabeculectomy throughout, while the right eye require multiple 5FU needling and antiglaucoma medications. Despite that IOP in the right eye was uncontrolled with IOP as high as 56mmHg.

A Xen tube insertion was initially performed 3 years prior. Over a period of 2 years after Xen tube insertion, IOP in the right eye was well controlled until subconjunctival fibrosis limits the IOP control, despite multiple 5FU needling and antiglaucoma medication. Hence, the decision for Baerveldt

implantation was made. The intraluminal stent was inserted into the drainage tube using Supramid<sup>R</sup> 3-0 suture. The stent was removed three months later to allow better IOP control.

Five months post stent removal patient presented with a complaint of worsening right visual acuity, with best-corrected visual acuity (BCVA) of 1/60, a drop from 6/24. Examination showed multiple deposits and fibrin on the anterior surface of his intraocular lens, with a significant presence of giant cells (Figure 1). However, no anterior chamber cells or flare were observed. The IOP was 10mm Hg. Topical corticosteroid, dexamethasone 0.1 % four times a day was started to treat the inflammation.

On a subsequent visit to the eye clinic 2 weeks later, the patient claimed that his right vision was better. His right BCVA improved to 6/60. The deposits on the anterior surface of the intraocular lens were notably lesser ( Figure 2a). There was no anterior chamber cells or flare. His right BCVA further improved to 6/28, slightly less than his best visual acuity 2 weeks later (Figure 2b).

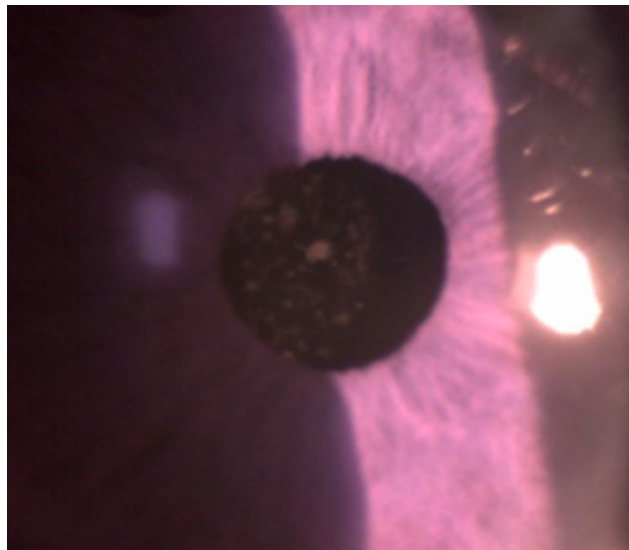


Figure 1: Presence of deposit and fibrin on the anterior intra ocular lens.

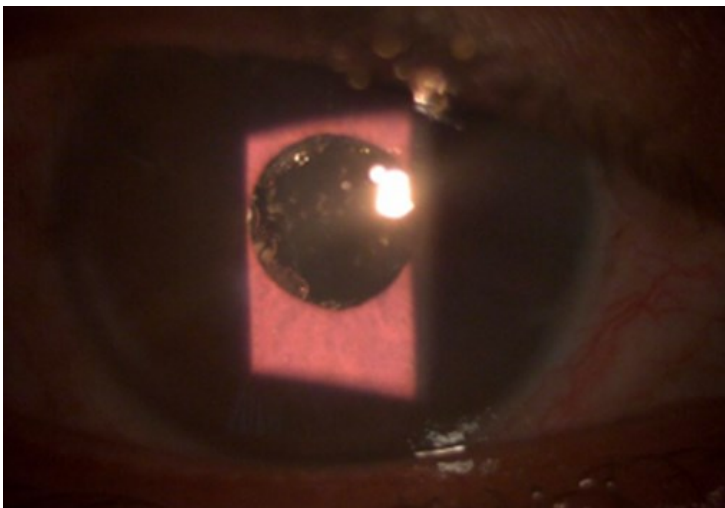


Figure 2a: Improved intraocular inflammation with less deposits on the anterior surface of the intraocular lens.



Figure 2b: Notable lesser deposits on the anterior surface of the intraocular lens.

## DISCUSSION

This case report highlights the occurrence of intraocular inflammation and intraocular lens deposit induced by removal of supramid stent from the Baerveldt tube using a ripcord technique. We think this is probably attributed by the disturbance in blood ocular barrier induced by the removal of the supramid stent which caused relative hypotony. The blood-ocular barrier consists of blood aqueous barrier (BAB) and blood-retinal barrier (BRB). The BAB is composed of the endothelial cells of the blood vessels in the iris and the non-pigmented cell layer of the ciliary epithelium [7]. The Blood retinal barrier (BRB) is formed by tight junctions between the endothelial cells of the retinal vessels (the inner BRB) and by similar tight junctions in the retinal pigment epithelium (the outer BRB) [7].

Ocular hypotony is known to cause a breakdown of the blood-aqueous barrier by the opening of the non-fenestrated endothelial layer of the iris vessels and the intercellular junctions of the ciliary body, alongside an increase in episcleral venous pressure. In addition, ocular hypotony leads to alterations in the intercellular tight junctions of the RPE and vascular endothelial cells, resulting in a breakdown of both the inner and outer blood-retinal barriers [8].

The breakdown of blood-ocular barriers allows inflammatory mediators, cells and proteins to enter into intraocular chambers and ocular tissues. Eyes with anterior uveitis have a reduction of the intercellular junctions in the ciliary epithelium. In addition, junctional disruptions, likely resulting in an increase in vascular permeability have been found in inter-endothelial junctions of the iris vessels in the eyes [8]. Macrophages, polymorphonuclear leukocytes and lymphocytes can thus elicit the inflammatory response and play a key role in the initiation of the uveitis process [8].

Deposits form on the intraocular lens in our case, were likely giant cells, visible on slit lamps as sharp, round, or oval spots with or without pigmentation [9]. Of note, a good response was seen in this patient towards topical steroids in resolving the intraocular lens deposit, as topical corticosteroids have been shown to facilitate and improve the blood aqueous barrier [10]. The use of topical corticosteroids as prophylaxis prior intraluminal stent removal is highly recommended to reduce the possible inflammation following the procedure which could worsen the visual outcome.

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## Case Report

### ACUTE SUBMACULAR HAEMORRHAGE: A CASE OF EARLY SPONTANEOUS DISPLACEMENT

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choroidal neovascular membrane

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#### ABSTRACT

*A case report of submacular haemorrhage that spontaneously displaced within 24 hours, thereby improving visual acuity. A case of subretinal haemorrhage over the macula of the right eye was presented to the eye clinic. The visual acuity of the affected eye was "counting fingers" at presentation. The patient was asked to return the next day for a pneumatic displacement of subretinal blood and was instructed on how to properly propped her head at home. Visual acuity of the affected eye improved dramatically to 6/24 the next day. Fundus examination showed a smaller submacular haemorrhage which was away from the foveal area. A pigment epithelial detachment was identified superior to the macula. Fundus fluorescein angiography showed a pulsatile hyperfluorescent spot near the macula with branching vascular network. A diagnosis of submacular bleed secondary to polypoidal choroidal vasculopathy (PCV) was made, and the patient was treated with intravitreal aflibercept. Submacular hemorrhages secondary to PCV can affect the vision severely and while the natural progression is variable, the vision can be improved simply by proper and adequate positioning of the patient's head to relocate the accumulation of the blood away from the fovea.*

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#### INTRODUCTION

Subretinal hemorrhage occurs when there is bleeding originating from the choroidal and/or the retinal circulation. The blood collects in a potential space between the neurosensory retina and the retinal pigment epithelium (RPE). The hemorrhages of choroidal origin may arise directly from the choriocapillaries via discontinuities in the Bruch's membrane, or from choroidal neovascular membranes (CNVs) which proliferate through breaks in the Bruch's membrane.

#### CASE REPORT

A 62-year-old lady presented with a sudden onset of loss of vision in the right eye. It was painless and affected the central field of vision. It was not preceded by floaters or flashes of light. Best-corrected visual acuity (BCVA) was 6/12 in the left eye and counting fingers in the right eye. Anterior segment examination revealed a nuclear sclerotic cataract in both eyes. There was no relative afferent pupillary defect detected. Fundus examination revealed a large dense subretinal haemorrhage in the posterior pole involving the macula and extending to the superior and inferior vascular arcades (Figure 1). The optic disc was

visible and pink in color with apparently healthy neuroretinal rim. An Optical Coherence Tomography confirmed the haemorrhage to be subretinal (Figure 2). She was planned for pneumatic displacement of the subretinal blood the next day. Instructions on how she ought to prop up her head while at home were clearly demonstrated to her. On her return to the clinic the next day, the visual acuity of her affected eye showed a dramatic improvement to 6/24 from the previous "counting fingers". On further inquiry, she attested that she had followed the instructions to keep her head propped up at all times, as directed.

Fundus examination showed a smaller area of subretinal haemorrhage which was away from the foveal (Figure 3). A pigment epithelial detachment was identified superior to the macula. Fundus fluorescein angiography showed a pulsatile hyperfluorescent spot near the macula with branching vascular network (Figure 4). A diagnosis of Acute submacular haemorrhage secondary to polypoidal choroidal vasculopathy (PCV) was made. Following confirmation with Indocyanine green angiography, patient was subsequently treated with intravitreal aflibercept. Her right BCVA remained good, 6/12 at six months follow up.

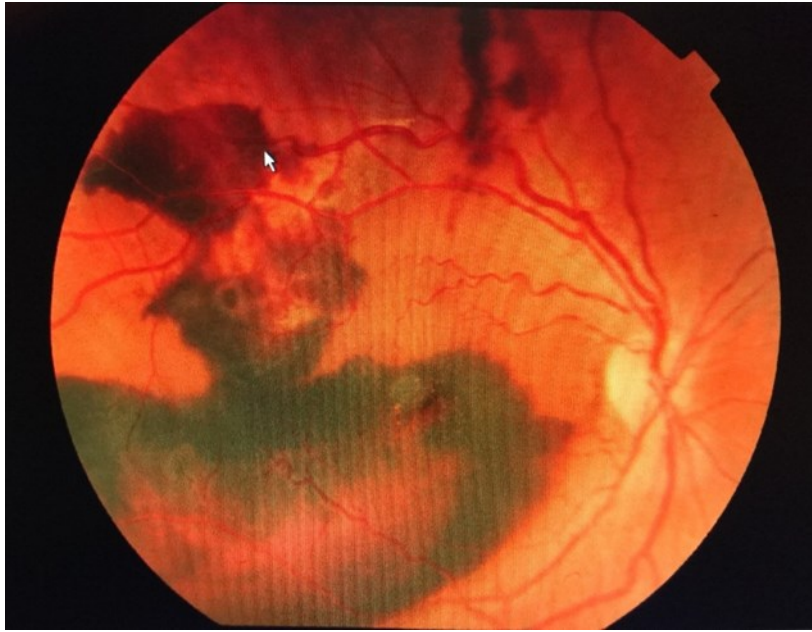


Figure 1: Right fundus photograph showing submacular haemorrhage at the initial presentation.

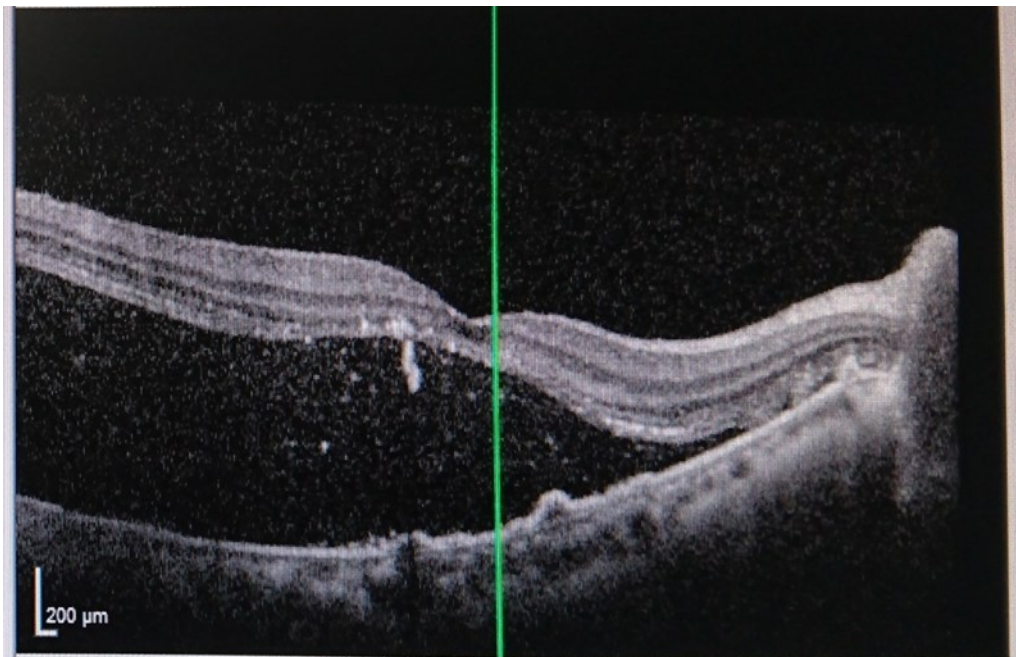


Figure 2: Optical Coherence Tomography showing subretinal haemorrhage involving the foveal region and RPE detachment.

## DISCUSSION

Subhyaloidal or macular haemorrhages are known to occur secondary to retinal or choroidal vascular diseases. The pathology include arteriosclerosis, hypertension, retinal vessel occlusion, diabetic retinopathy, chorioretinitis, retinal microaneurysm, age-related macular degeneration and several other blood disorders [1]. The condition may also be precipitated by trauma or occur spontaneously.

As a result of the location of the haemorrhage at the macula, patients usually experience a sudden occurrence of reduced vision. Visual acuity may

deteriorate within seconds to minutes [2]. However, in patients who have a concurrent subfoveal disciform scarring, a condition which is often related to eyes with age-related macular degeneration, the haemorrhage itself may go unnoticed as the patient's visual acuity may be limited to begin with [3]. Similarly, a subretinal haemorrhage which occurs away from the fovea could present with minimal symptoms and preserve the patient's central vision. Other symptoms of visual deterioration in association with macular hemorrhages include a visual field defect with or without metamorphopsia [4].





Figure 3: Fundus photograph one day after the presentation: The subretinal haemorrhage is inferiorly displaced.



Figure 4: Fundus Fluorescein Angiography of the right eye documenting a polyp as a hyperfluorescent spot in the macula area supero-temporal to the fovea.

In fundusoscopic examination, submacular hemorrhages appear as an elevation of the overlying neurosensory retina which may be associated with retinal folds. The borders of the hemorrhage are usually sharply demarcated, resulting in a dome-like shape in the area of hemorrhage [5]. The colour of the blood within the hemorrhage may vary, ranging from bright or dark red in early stages, or yellow or tan in later stages once the blood content becomes devoid of its haemoglobin content [6].

Without active intervention, the hemorrhage may undergo spontaneous reabsorption, a process that could take a duration of 1 to 2 months duration [7]. This scenario carries the risk of permanent visual loss from irreversible retinal damage caused by the formation of pre-retinal tractional membranes and proliferative vitreoretinopathy as well as the toxic effect of longstanding hemorrhage to the photoreceptors [5]. Submacular hemorrhages thus carry a poorer prognosis of visual recovery compared to subhyaloidal hemorrhages for these particular reasons [8].

Hayasaka et al retrospectively reviewed 24 eyes with pathologic myopia and subretinal hemorrhage and found that the subretinal hemorrhage spontaneously reabsorbed within 1 year in 15 eyes without CNV, with the visual acuity improving or remaining unchanged [9]. The visual acuity was unchanged or worsened in 9 other eyes which had CNV without AMD. A non-consecutive retrospective study by Berrocal et al showed spontaneous improvement in visual acuity correlating to spontaneous reabsorption of subretinal hemorrhage over a period of 3 to 56 months [10]. The eyes with AMD-related subretinal hemorrhages were more likely to improve compared to those that were not AMD related. Another non-consecutive retrospective study by Bennet et al reviewed 29 cases of subretinal hemorrhage of at least one disc-diameter in size resulting in visual loss [11]. Cases were reviewed over an average period of 3 years. Mean visual acuity was seen to improve more in cases that were not AMD related, while AMD related eyes showed no improvement. In addition, eyes with a thick subretinal hemorrhage carried a worse visual prognosis and the final visual acuity correlated with the size of the initial subretinal hemorrhage.

Based on the preceding studies, there is a variable natural history of subretinal hemorrhage [12]. Treatment of the condition must therefore aim to remove the hemorrhage before any permanent retinal damage manifests. Observation of the condition for spontaneous clearing of the hemorrhage is a clinically accepted practice up to a duration of 3 months, although early surgery can also be considered within this time period.

Among the treatment modalities for submacular hemorrhages include laser drainage, also known as laser membranotomy and laser puncturing. This technique was introduced by Heydenreich and Fechner in 1973 [13]. This treatment has been recommended for use within the first 3 to 4 days after the onset of hemorrhage and works by

creating a focal opening into the vitreous cavity through which the entrapped blood may drain [14]. A common complication of this procedure is the formation of epimacular membranes which are theorized to occur due to the presence of growth factors responsible for stimulating proliferation of entrapped cells between the inner limiting membrane (ILM) and the retinal surface. Formation of macular hole and retinal detachments are rarely reported. Recombinant tissue plasminogen activator and gas has also been used in management of submacular hemorrhages where drainage of the blood was achieved via separation of the vitreous [15].

Immediate and complete removal of the hemorrhage can be accomplished via vitrectomy, with the added benefit of prompt recovery of vision. De Maeyer et al treated 5 cases of submacular hemorrhage with excellent visual recovery in all subjects [16]. Intraoperatively, the location of the hemorrhages were all identified as sub-ILM, which was achieved by ILM biostaining [17]. Timely vitrectomy may also prevent irreversible retinal damage which could potentially arise from a longstanding hemorrhage. The procedure carries a number of risks and side effects which should be informed to the patient prior to surgery. This includes cataract formation, intraoperative breaks and postoperative proliferative vitreoretinopathy which may result in a retinal detachment, necessitating a second procedure [18,19].

In summary, submacular hemorrhage can result in a sudden severe drop in vision and several methods can be applied for its management. Spontaneous reabsorption or relocation of the hemorrhage may occur in the early period of the disease, but the natural progression without treatment is variable. Vitrectomy has shown good results in prompt clearing of the hemorrhage with good potential recovery of vision, while laser drainage has also achieved good functional results. In patients who present with severe visual loss at the outset, a simple procedure like the positioning of the head is recommended. This is to attempt relocation of the site of accumulated blood to an area that spares visual loss.

## CONCLUSION

Submacular hemorrhages secondary to PCV can affect the vision severely and while the natural progression is variable, the severity may be improved upon simply by proper and adequate positioning of the patient's head. This procedure is non-invasive, inexpensive, and without any ill effects.

## PATIENT CONSENT

Consent to publish the case report has been obtained from the patient. The anonymity of the patient is preserved in this report

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